Depression and cancer: physiological and psychological markers

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Depression and Cancer:
Physiological and Psychological Markers

PhD Thesis

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Abstract

Aim: To investigate potential markers for depression and poor quality of life (QoL) in head and neck (HN) and colorectal (CR) cancer patients.

Background: Comorbid depression is strongly related to decreased QoL in cancer patients and may increase the risk of mortality. Many psychosocial factors, such as childhood trauma (CT), neuroticism (NE), past history of depression (PH) and current life events (LE) increase the risk of depression. Depression is also associated with increased levels of pro-inflammatory cytokines and patients with comorbid depression and cancer show higher levels compared to patients with either condition alone. Thus, increased inflammation may also be a risk factor for low mood. This thesis explores relationships between inflammation and psychosocial risk factors and their potential as predictive markers for depression in cancer patients.

Methods: Ninety-one newly diagnosed cancer patients due for surgical treatment (57 HN and 34 CR) completed the Hospital Anxiety and Depression Scale and European Organisation for Research and Treatment of Cancer QoL Questionnaire before surgery and one, three and six months following surgery. Patients gave blood samples before and one week and one month after surgery to measure levels of C-reactive protein and pro-inflammatory cytokines and saliva samples before surgery. The Brief Life Events Questionnaire was completed at one month and the Eysenck Personality Questionnaire, Childhood Trauma Questionnaire and Brief COPE at three months. Patients completed a diagnostic interview between three and six months for diagnosis of past or current episode of depression.

Results: Childhood trauma, NE, PH and LE were all related to low mood and poorer QoL. Increased inflammation was associated with lower mood post treatment in CR patients, but there were fewer associations in the HN patients.

Conclusions: Both psychosocial and inflammatory markers are related to lower mood after treatment. PH is a simple but informative marker for increased risk of depression in cancer patients.

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[1] Klineberg E (2009) Collective term for those involved in social support during thesis submission. Personal communication.

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List of Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotrophin Releasing Hormone
BLEQ	Brief Life Events Questionnaire
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disorders
CR	Colorectal
CR29	EORTC-QLQ Colorectal module
CRH	Corticotrophin Releasing Hormone
CRP	C-Reactive Protein
CT	Childhood Trauma
CTQ	Childhood Trauma Questionnaire
cv	Coefficient of variation
DD	Depressive Disorder
DE	Depressive Episode
DE6	Depressive Episode within six months
DST	Dexamethasone Suppression Test
ELS	Early Life Stress
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPQ	Eysenck Personality Questionnaire
EPQ-N	Eysenck Personality Questionnaire – Neuroticism scale
H&N35	EORTC-QLQ Head and neck module
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety scale
HADS-D	Hospital Anxiety and Depression Scale – Depression scale
HN	Head and Neck
HPAA	Hypothalamic-Pituitary-Adrenal Axis
HPV	Human Papilloma Virus
IFN	Interferon
IL	Interleukin

Abbreviation	Definition
LE	Life Events
MD	Major Depression
MDD	Major Depressive Disorder
N stage	Measure of lymph node metastases according to UICC TNM staging
NE	Neuroticism
OR	Odds Ratio
PH	Past History
PMHS	Past Mental Health Screening Questionnaire
QoL	Quality of Life
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
sd	Standard deviation
T stage	Extent of tumour according to UICC TNM staging
T1	Time 1 – baseline
T2	Time 2 – one week post primary treatment
T3	Time 3 – 6-8 weeks post primary treatment
T4	Time 4 – 12-14 weeks post primary treatment
T5	Time 5 – 26 weeks post primary treatment
TNF	Tumour Necrosis Factor
TNM	Tumour Node Metastasis
UICC	International Union Against Cancer

Overview

Both cancer and depression are common conditions in the UK: 293,601 people were diagnosed with cancer in 2006 and 2.6 million people were diagnosed with depression in 2000 and probably many more remained undiagnosed[1-3]. Comorbid depression is often assumed to be highly prevalent among cancer patients, and is associated with poorer quality of life[4], and some evidence of increased mortality[5]. Despite these negative consequences, depression is also reported to be under treated and under diagnosed in many cancer clinics[6, 7]. The aims of this thesis are to:

1. Measure the prevalence of depressive disorders in two cancer clinics.
2. Explore what factors might increase the risk of developing a depressive episode in cancer patients.

This is so future patients who are at an increased risk of developing depression can be monitored and provided with appropriate support to improve their treatment outcome.

The thesis comprises two complementary studies:

1. A quantitative cross sectional study.
2. A multidisciplinary prospective study.

Both of the studies are conducted on colorectal cancer patients recruited from The Royal London Hospital and head and neck cancer patients recruited from St Bartholomew's Hospital.

The cross sectional study investigates the prevalence of depressive symptoms and point prevalence of a depressive episode in the respective clinics. The results from some exploratory analyses investigating the relationship between depressive symptoms and quality of life are also presented.

The greater part of this thesis focuses on the prospective study. This study investigates potential physiological and psychological markers of depression in order to explore what factors might increase the risk of development of a depressive disorder in cancer patients soon after their diagnosis.

The cross sectional study and the prospective study have been presented in different ways. Also, due to the inter-disciplinary nature of the prospective study a review of a substantial amount of literature is required. As a result in order to present the contents in the most comprehensive manner the thesis has been split into four parts:

1. Background
2. Cross sectional study
3. Prospective study
4. General discussion

The background is an introduction to the relevant literature on cancer and depression and provides the context of the thesis within medical research. It presents the rational to the hypotheses and the methodology of the studies. The

more technical aspects to the literature are presented with the relevant aspects of the study. Similarly, a technical discussion is included in each of the results chapters. The findings are reiterated in the general discussion and presented in the context of clinical implications and further research.

The cross sectional and prospective study are presented in different formats. The cross sectional study is presented in two chapters; firstly an introduction and methods, secondly the results and discussion. The prospective study is presented in six parts; the methods and five results chapters: 1) the sample, 2) psychological factors, 3) physiological factors, 4) covariates and 5) adjusted models. Each results chapter is accompanied by an introduction, results and discussion, and an additional methods section in the final results chapter. The aims of the chapters are:

1. Summary – introduce the data set and report prevalence of mood disorders.
2. Psychological factors – test for associations between psychological risk factors and later depressive symptomatology and poorer quality of life.
3. Physiological factors – test for associations between physiological risk factors and later depressive symptomatology and poorer quality of life.
4. Covariates – test for associations between physiological and psychological risk factors and justify need for adjusted models
5. Adjusted models – present adjusted models for risk of depressive symptomatology and poorer quality of life.

Wherever possible the findings from each chapter are linked to previous chapters in order to build on the overall conclusions of the thesis, which are then brought together in the final discussion. Please see figure 0.1 for a diagram of the thesis structure.

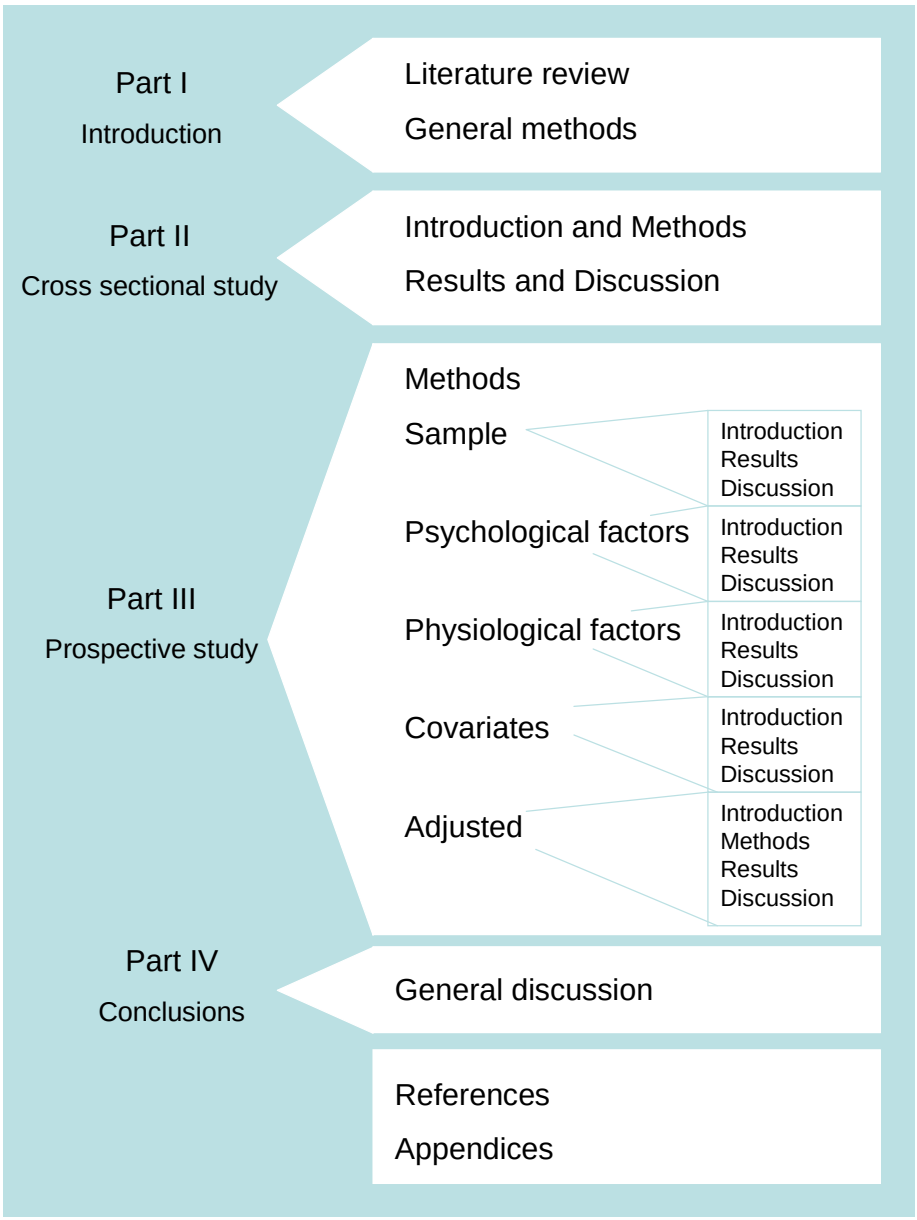
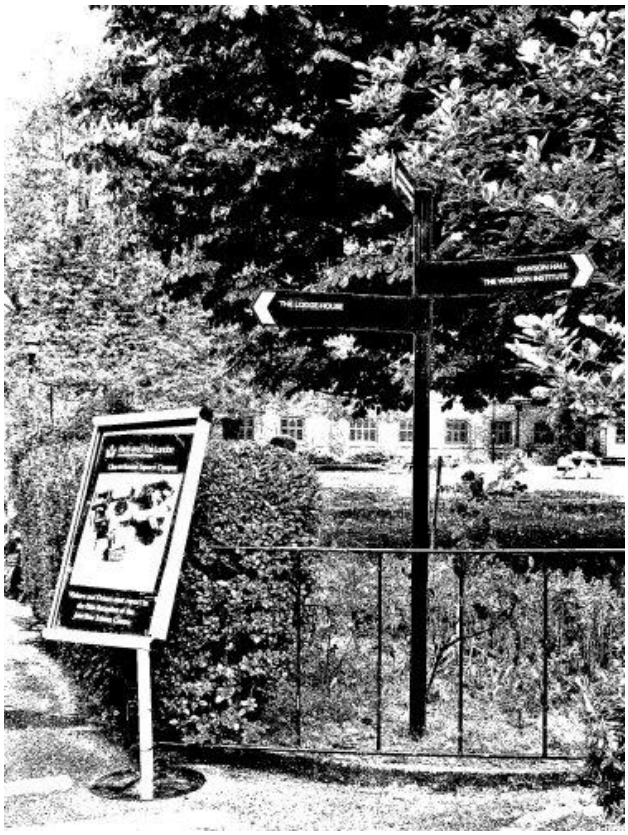


Figure 0.1: Thesis outline

PART I

Literature review



1 Literature review

This section introduces the background and rationale for the hypotheses and methodology underlying this study. Firstly, an overview of the classification and treatment of head and neck (HN) and colorectal (CR) cancers and diagnosis and measurement of depression are covered. The review then focuses on the associations between depression and cancer: i) prevalence of depression in cancer patients; and ii) consequences of comorbid depression on cancer treatment outcome. The review is limited to areas relevant to the thesis title. However, where only limited data exist on HN or CR cancer, results from heterogeneous cancer groups are also included.

1.1 Cancer

"Cancer" is an umbrella term that covers a wide range of different diseases in which cells undergo genetic mutation and continue dividing uncontrollably. Cancer can occur in any cell and create a tumour which does not spread (benign) or which can be locally invasive or metastasize to different organs (malignant)[8].

The risk factors for cancer, including genetic risk, vary greatly depending on the type and location of the cancer. Similarly, the treatment and prognosis vary according to the site and stage. Head and neck, and CR cancers are two distinct types of cancer, affected by different risk factors and with different consequences on quality of life (QoL). The inclusion of such disparate cancers allows for comparison between different cancer groups.

1.1.1 Colorectal cancer

Colorectal cancer includes malignancies of the colon or rectum. According to Cancer Research UK[9] CR cancer is the third most common form of cancer in the UK, with 29,565 new cases reported in 2005. Around two thirds of all cases are of the colon, the rest are rectal. The cancers can be either squamous cell carcinomas or adenocarcinomas.

Most solid tumours are staged using the universal TNM staging by the International Union Against Cancer (UICC) to indicate the extent of disease. TNM stands for tumour, node and metastasis. T stage indicates the extent of the tumour and scores range from zero to four; N stage indicates the number of lymph node metastases and scores range from zero to a maximum of four (depending on the cancer site) and M is either zero or one (one indicating the presence of one or more metastasis). The grading of the T and N aspects depends on the tumour

site. For CR cancer patients the tumour and node status are allocated as follows[10] (see figure 1.1 for cross section diagram of the intestine).

Tumour status:

T1: Tumor invades submucosa.

T2: Tumor invades muscularis propria.

T3: Tumor invades through the muscularis propria into the subserosa, or into the pericolic or perirectal tissues.

T4: Tumor directly invades other organs or structures, and/or perforates.

Nodal status:

N0: No regional lymph node metastasis.

N1: Metastasis in 1 to 3 regional lymph nodes.

N2: Metastasis in 4 or more regional lymph nodes.

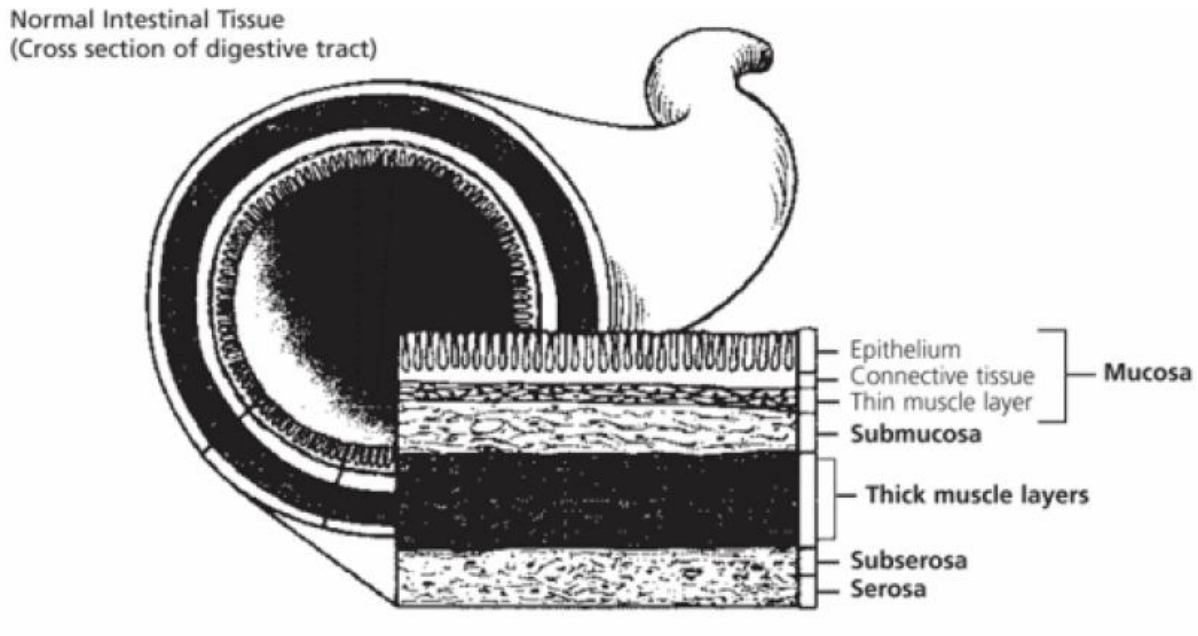


Figure 1.1: The layers of the colon wall. Reprinted by the permission of the American Cancer Society, Inc. from www.cancer.org. All rights reserved

1.1.1.1 Risk factors

As with HN cancer there are genetic, lifestyle and some predisposing diseases that increase the risk of developing CR cancer. Familial adenomatous polyposis and hereditary non-polyposis CR cancer, Human Papilloma Virus (HPV) (squamous anal carcinoma only), inflammatory bowel diseases (Crohn's and ulcerative colitis) all increase the risk of CR cancer. However, the pathway to carcinogenesis appears to differ in these cancers compared to sporadic carcinomas and most CR cancers are sporadic[11, 12]. Inflammatory bowel diseases (IBD) confer an increased risk of 0.5-1% per year[13] compared to a 2x greater risk of CR cancer if one immediate family member suffered from CR cancer[14]. Despite the hereditary aspect to CR cancer, at the time of writing, there is less conclusive evidence for individual genes[15].

The behavioural risk factors for CR cancer are not as well defined as those for HN cancer. Alcohol is considered to confer a moderate risk[16] though this was not significant for higher rectal tumours. There is still some debate about whether smoking increases the risk of CR cancer; Paskett and colleagues (2007)[17] found evidence of an increased risk in US female current smokers in a prospective cohort study. However, a review by the International Agency for Research on Cancer[18] recently reported that the effects are so small that they could be due to poor control for other associated risks, although they do not give any information on the studies included in their review or their respective findings.

It has been suggested that dietary factors play a role in the aetiology of CR cancer. Norat *et al*. (2005)[19] found an increased risk for red meat intake of over 100g/day, as supported by a previous meta-analysis by the same author[20]. Many studies and some reviews have found an increased risk of CR cancer in people with a body mass index (BMI) of over 30[21-23].

1.1.1.2 Treatments

The main treatment for CR cancer is surgical resection, which in some cases may be accompanied by either preoperative or adjuvant chemotherapy. People with rectal cancer may also receive radiotherapy. Patients with advanced stage bowel cancer may be treated with primary chemotherapy. Also, some patients may require a colostomy or ileostomy. In most cases this is temporary, to let the bowel heal. However, in a small number of patients a permanent colostomy is necessary. This is more common in rectal tumours than colon cancer (roughly 41% and 7% respectively[24]).

A course of chemotherapy typically takes about two months. In this time the patient will alternate between drug and recovery phases (allowing tissue repair during the rest periods). Chemotherapy results in severe fatigue and may be accompanied by: fever and chills, skin changes, feeling weak, loss of appetite, dry mouth and/or ulcers, taste changes and changes in nails and possibly nausea and vomiting, hair loss or sensitivity to sunlight. Radiotherapy involves 15 minute hospital visits for five days a week for between three and seven weeks. The side effects are fatigue and soreness of skin around the treated area and possibly nausea.

1.1.1.3 Prognosis

For each type of cancer there are two main aspects to prognosis: length of survival and QoL. A patient's prognosis is affected by the size and site of the tumour as well as by their general health (which will also determine their treatment).

1.1.1.3.1 Mortality

Colorectal cancer is the second most frequent cause of cancer death in the UK[9] causing 16000 deaths in the UK in 2005. However, the high death rate is mainly

due to high incidence rates and in fact 46% of patients are still alive 5 years after their diagnosis[9].

1.1.1.3.2 Quality of life

Colorectal cancer patients may suffer from a brief period of poor bowel function, but generally most can expect their QoL to return to levels similar to that of the general population[25-27]. Patients with a stoma have to adapt to using a colostomy bag. A recent review reported that use of a stoma led to a decrease in QoL[28]. However, perhaps counter-intuitively, a meta-analysis and Cochrane review both report that stomata appear to have little impact on long term QoL when compared to anterior resection for rectal cancer[29, 30].

All types of cancers are associated with a risk of 'sickness behaviour'[31]. This syndrome is characterised by depressed mood, decreased appetite, weight loss and fatigue and many symptoms that overlap with depression (see table 1.1). This obviously affects the QoL of any cancer patient. Sickness behaviour is considered to be related to inflammation secondary to the tumour. Physical trauma, such as surgery or radiotherapy, increases the levels of inflammatory mediators in the blood. These include molecules known as cytokines that have been shown to induce the symptoms of sickness behaviour[31] (the role of cytokines is reviewed in more depth in section 1.2.4.2.) Sickness behaviour is also known to increase the risk of experiencing a depressive episode (DE). However, not everyone who suffers from sickness behaviour develops a DE and it has been suggested that vulnerability to a depressive disorder (DD) increases the risk of a DE following cytokine-induced sickness behaviour[31].

Major Depression	Sickness Behaviour
Depressed mood	Depressed mood
Anhedonia	Anhedonia
Decreased appetite	Decreased appetite
Weight loss	Weight loss
Sleep disturbances	Sleep disturbances
Psychomotor retardation	Psychomotor retardation
Decreased libido	Decreased libido
Fatigue	Fatigue
Cognitive problems	Cognitive problems
Guilt/worthlessness	Flu-like symptoms
Suicidality	

Table 1.1: Comparison of major depression and cytokine-induced sickness behaviour

1.1.2 Head and neck cancer

The term HN cancer includes malignancies of the:

- Mouth (hard palate, soft palate, tongue, floor of mouth, tonsils, uvula, oropharynx, mandible, maxilla and salivary glands)
- Nose (nasal cavity, nasopharynx and paranasal sinuses)
- Throat (pharyngeal wall, larynx, pharynx, oesophagus and thyroid)

See figure 1.2 for cross section of HN anatomy.

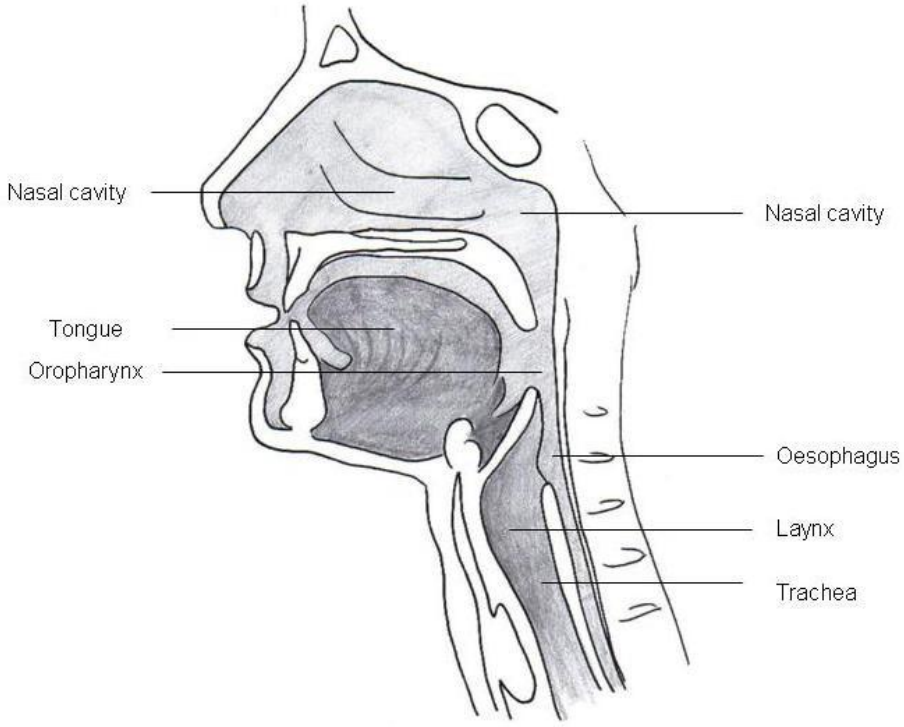


Figure 1.2: Head and neck anatomy diagram

According to cancer research statistics, HN cancer is the 16th most common form of cancer (laryngeal cancers are 20th) with just over 4,500 new cases of oral cancer in the UK in 2005[2]. The incidence increases dramatically when laryngeal and oesophageal cancers are included; 12,725 new HN cases were reported in 2005 in the UK[2]. Most malignancies (90% of oral cancers[32]) are squamous cell carcinomas, the rest are sarcomas or adenocarcinomas.

TNM staging can also be used in HN cancer, where the M staging is the same. There are many sites within the HN umbrella and the precise staging varies according to the site, but broadly speaking the T and N stagings are defined as follows:

Tumour:

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 2 cm or less in greatest dimension
- T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3: Tumor more than 4 cm in greatest dimension
- T4: Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin. Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4)

Node involvement:

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N3 Metastasis in a lymph node more than 6 cm in greatest dimension

1.1.2.1 Risk factors

There have been reports on genetic polymorphisms leading to an increased risk of HN cancer[33] as well as social factors and HPV[34]. The risks for HN cancer for which there is most evidence are behavioural factors, such as tobacco and alcohol use[32]. There are less conclusive risks such as low fruit and vegetable intake and

low BMI. HPV confers a considerable risk and approximately 20% of HN cancers are HPV positive[34, 35].

By far the biggest risk factor for development of HN cancer is use of tobacco: cigarettes, pipes or chewing tobacco or betel nut (with or without tobacco) all substantially increase the risk of HN malignancies[36]. Over 90% of oral cancer patients use tobacco in some form[32], and a study by Rodriguez *et al*. (2004)[37] found that even smoking fewer than 15 cigarettes a day increased the odds of developing cancer by 4.37 compared to never having smoked. Similarly, Freedman *et al*. (2007)[38] reported an odds ratio of 6.65 for men and 16.17 for women smoking more than 20 cigarettes/day.

The second biggest risk is use of alcohol; 75-80% of HN patients drink alcohol regularly[32]. From the same sample Freedman *et al*. (2007)[39] found that over three alcoholic drinks a day increases the risk of HN cancer. Likewise Rodriguez *et al*. (2004)[37] found that drinking between 6-10 drinks per day increases the risk of HN cancer by 3.69, but they found no increased risk for fewer than six drinks a day. However the risk conferred by alcohol is much weaker in the absence of tobacco use[40]. There is a greatly increased risk with combined alcohol and tobacco use[37, 41], but alcohol and smoking are not associated with HPV related pharyngeal cancers[42]. Other much smaller, though still significant, risks include low intake of fruit and vegetables[43] and low BMI[44-46].

Finally, it should be noted that all of these environmental risks are usually associated with each other. For example, alcohol consumption is associated with tobacco use[47] as well as poor nutrition (decreased intake, impaired metabolism and poor absorption)[48]. Also, the associations vary by cancer site even within the umbrella term of HN cancers. For instance the increased risk of malignancy from smoking is strongest for cancers of the larynx[40].

A point of particular relevance to this study is that all of these risk factors are also more common in patients with a DD[49].

1.1.2.2 Treatments

Cancer treatment varies according to the site and stage of the tumour. Surgery is usually the first choice for treating HN tumours, but sometimes the tumour is considered to be technically impossible to resect, or the result would be functionally too disabling. Also, some patients are not fit enough to cope with the physical trauma of surgery. The amount of disability and recovery time after surgery depends on the tissue removed; this can range from a day in hospital with no long term impairment to a hospital admission lasting months or permanent effects such as complete loss of voice.

When surgery is contraindicated, primary chemotherapy and/or radiotherapy are offered. The side effects of chemotherapy are similar to those of the CR patients. Similarly HN patients undergoing radiotherapy can expect side effects including fatigue and soreness of skin around the treated area, as well as sore throat and mouth, dry mouth, dental complications and halitosis, loss of taste and appetite, jaw stiffness and possibly hair loss. Many patients undergo more then one modality of treatment in order to minimise the possibility of recurrence without long term loss of function. Often patients are offered radiotherapy after an operation to eradicate undetected cancer cells. Occasionally a patient is offered surgery after radiotherapy and chemotherapy treatment. This may be because the tumour is very large and would be resectable if the patient responds well to chemo- or radiotherapy. However, sometimes if the tumour is not controlled by chemo- or radiotherapy a patient may be offered ‘salvage surgery’. This refers to unplanned surgery, but it is associated with poorer prognosis[50]. The side effects are fatigue and soreness of skin around the treated area, throat and mouth, dry mouth, dental complications and halitosis, loss of taste and appetite, tiredness and jaw stiffness and possibly hair loss and nausea.

It is notable that thyroid cancers are treated by thyroidectomy even before confirming the diagnosis and removal of the thyroid gland affects endocrine function, resulting in additional complications. For these reasons, thyroid cancer is considered to differ from other HN cancers and is not included in this thesis.

1.1.2.3 Prognosis

1.1.2.3.1 Mortality

The 2 year all cause survival rate for oral cavity malignancies is estimated at 62%[32] and 5 year relative survival for all HN malignancies is estimated at 52.5%[51].

1.1.2.3.2 Quality of life

As well as having to deal with a life threatening illness, a person with HN cancer may suffer impairments of speech, eating, aesthetics, pain and social function. Surgery to the mouth may cause numbness, poorer opening and/or loss of teeth. If the patient undergoes a neck dissection then the extent of the dissection will further affect their QoL due to neck and shoulder pain and restricted range of movement[52]. Patients undergoing a laryngectomy must learn other ways to communicate. Of particular relevance to HN patients (compared to CR patients) is the likelihood of potentially obvious and difficult to conceal disfigurement (figure 1.3)[53, 54]. However, whilst some patients do experience great disfigurement, the majority of patients do not. Also, although some studies have found a relationship between greater disfigurement and increased distress[55], others have failed to find an association between level of disfigurement (both patient perceived and surgeon rated) and QoL[54]. One study found an association, but only in those with low social self-efficacy[53], suggesting the relationship is dependent on other factors. It has also been suggested that a lack of an association between distress and

disfigurement is because the disfigurement is seen as an inevitable trade off between life and death[54].

Figure 1.3: Head and neck cancer patient. Picture provided by The Facial Surgery Research Foundation.

1.1.3 Comparing head and neck, and colorectal cancer

	HN cancer	CR cancer
Prevalence	Almost 5,000 new cases each year in the UK	Over 35,000 new cases each year in the UK
Risks	Smoking and alcohol substantial risk factors	Risk factors still inconclusive
Treatment	Varied. Ranges from simple operation to complicated operation and chemotherapy and/or radiotherapy	Usually resection, sometimes adjuvant chemotherapy is offered and/or radiotherapy for rectal cancer patients
Mortality	5 year survival 56%	5 year survival 46%
Possible functional limitations	Speech (10%), difficulty eating/drinking (swallowing 15%, chewing 18%), restricted mouth opening/movement, dry mouth, loss of taste, pain (34%), disfigurement (32%)*	Permanent colostomy, diarrhoea (14-49%), constipation (7%), incontinence (39%) bloating, pain.

Table 1.2: Comparing HN, and CR cancer. * percentages given are proportion of patients reported to have moderate or severe problems as reported in a group of 68 HN patients and a review of CR symptoms[56, 57].

1.2 Depression

1.2.1 Defining and assessing depression

It is important to define depression and to clarify the difference between depressive symptoms and DDs and how both are assessed and measured.

1.2.1.1 Depressive symptoms

Depressive symptoms are common, transient and experienced by most people at some point in their lifetime, especially in response to a stressor. Depressive symptoms are usually assessed with the use of a questionnaire such as the Hospital Anxiety and Depression Scale (HADS) or Centre for Epidemiological Studies Depression Scale (CES-D). These questionnaires are very useful in that they give an indication of how many symptoms are present at the time of completing the questionnaire. The questionnaires are brief and provide a useful screening tool for depression in clinical settings by drawing attention to patients who may be suffering from a DD. For instance, if a patient scored from 7-10 (out of 14) on the HADS depression subscale then they have a sufficient number of depressive symptoms to be considered as a possible case of depression, and a score of 11 or above is considered to be a likely case of depression[58]. In both cases the patient should be followed up and referred to psychological or psychiatric services if necessary. However, the questionnaires alone do not provide a diagnosis of a major DD.

1.2.1.2 Depressive disorders

A DD, such as major depression (MD), is a syndromal condition that is characterized by recurrent episodes of depressed mood and disturbed neurovegetative and cognitive functioning for a period of at least two weeks (see table 1.3) resulting in functional impairment. Major depression is generally reported to have a 12 month incidence of about 10%[59]. A DE has a point prevalence of 2.8% and mixed anxiety and DD has a point prevalence of 8.8% in adults living in private households in the UK[60]. Sufferers are more likely to be female with average age of onset between 20-30 years old[60].

Major depression often results in recurrent episodes of depression over the lifetime and once a person has experienced one DE they are much more likely to

experience another episode in the future. A structured clinical interview provides information on whether a minimum number of symptoms are present for a given duration above the threshold for a DE defined by a recognised categorical classification system (DSM-IV or ICD-10). Structured clinical interviews using DSM or ICD criteria should be conducted by a trained and standardised interviewer who can thus provide a robust assessment of a DD. Depressive disorders have a multifactorial aetiology involving both genetic and environmental components and occur in individuals who have an increased vulnerability to the effects of environmental stressors, often accompanied by dysregulation and hyper-reactivity of the stress hormone axis[61]. Episodes of MD in these individuals are often triggered by a stressful life event[62].

1.2.2 Aetiology of depression

There are psychosocial and biological theories of aetiology of depression. A full review is beyond the scope of this chapter, therefore it will focus on the biological and stress related aspects of depression that are particularly relevant to this study. However, it is important to note that genetic and psychosocial components are involved.

The current widely accepted view is that environmental stressors increase the risk of a DD in those who are vulnerable through genetic predisposition[62, 63] and most episodes of depression are precipitated by a stressful life event. Those with history of childhood trauma (CT) are more vulnerable[62].

A variety of twin and genome linkage studies have demonstrated that depression has a strong genetic component and certain genes e.g. the serotonin transporter linked promoter region (5-HTTLPR) have been shown to interact with environmental factors in the development of a DD[63-65]. There is also a genetic component to certain personality traits, particularly neuroticism (NE), which is a strong predictor of MD following a major stressor[62].

ICD-10	DSM-IV
Lowering of mood, reduction of energy, and decrease in activity. The lowered mood varies little from day to day and is unresponsive to circumstances. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Disturbed sleep. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. May be accompanied by: Early waking in the morning; several hours before the usual time. Depression worst in the morning. Marked psychomotor retardation. Agitation. Loss of appetite, weight loss. Loss of libido. Depending upon the number and severity of the symptoms, a DE may be specified as mild, moderate or severe.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. (1) depressed mood most of the day, nearly every day. (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. (3) significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day. (4) insomnia or hypersomnia nearly every day (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) (6) fatigue or loss of energy nearly every day (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (9) recurrent thoughts of death, recurrent suicidal ideation, plan or attempt.

Table 1.3: ICD and DSM-IV criteria for major DE.

There are many psychosocial aspects that are associated with depression; most notably MD patients are more likely to have lower social economic status[66], smoke[67], consume more alcohol[68], exercise less and are more likely to be obese[69]. Also, people suffering from MD are more likely to suffer from certain

physical illnesses such as coronary heart disease[70] and express fewer satisfactory forms of social support[71]. In some cases the lifestyle choices may be partly responsible for the increase in comorbidities, but the level of cause and effect has yet to be elucidated[70]. There is also evidence towards increased mortality in MD patients independent of the risk of suicide[72].

1.2.3 Psychological risk factors

Early life stress (ELS) is considered to be a major risk factor for the development of depression; Widom *et al*. (2007)[73] reported an odds ratio of 1.51 of current adult MD in adults who suffered from childhood abuse and/or neglect compared to controls. Early life stress includes physical, emotional and sexual abuse, as well as unstable families, poor parental care or dysfunctional relationships between the carer and child, as well as poverty and/or parental loss through death or separation[74].

Stressful life events (LE) also play a major role in the occurrence of a DD. Stressful life events are any events that result in considerable life change. Life events can be positive or negative (e.g. loss of job, death of a loved one, moving house or marriage) but negative stressful LE are stronger predictors of mental health outcome[75]. Some studies have shown that life stressors account for more of the variance (39%) in predicting depression than any other factor[76]. However, it is worth noting that one third of this variance is non-causal stress: for example, individuals at high risk of depression tend to select high stress environments and depression can cause stressful events (e.g. loss of job)[77]. In addition, as the number of DEs increases, future episodes are more likely to occur spontaneously or be preceded by a less pronounced stressor[75].

Many other psychological issues play a major role in depression, for instance how a person copes with stress, thought patterns and aspects of personality, such as NE. The background of these aspects is discussed further in chapter 7.

1.2.4 Physiological mechanisms

There is also robust neurophysiological evidence for the role of stress in depression, particularly findings reporting abnormalities in the stress hormone axis and inflammatory pathways in those with depression and those at increased risk of depression, e.g. highly neurotic individuals or those who suffered from ELS.

1.2.4.1 The Hypothalamic-pituitary-adrenal axis

One of the main components of the physiological stress response is the hypothalamic-pituitary-adrenal axis (HPAA) which, together with the autonomic nervous system enables the body to respond to stressors and to maintain homeostasis. The hypothalamus releases corticotrophin releasing hormone (CRH) in response to stress which causes the pituitary to release adrenocorticotrophic hormone (ACTH). ACTH controls the release of glucocorticoids from the adrenal glands (cortisol in humans and corticosterone in rodents), which stimulate the body ready for a fight or flight response. Cortisol also acts as its own negative feedback, such that circulating cortisol inhibits further release of ACTH from the pituitary and (independently) inhibits the release of CRH from the hypothalamus (see figure 1.4). In healthy individuals cortisol secretion shows a circadian rhythm with a night time nadir then a morning rise within the first half an hour after waking up, followed by a gradual decline throughout the day[78].

Dysregulation and hyperactivity of the HPAA is a robust finding in 50% of patients suffering from a DD[79, 80]. Many patients suffering from a DD show an increase in the daily mean cortisol expression, an increased morning rise[81] and increased evening activation[82]. This evidence is supported by animal studies using animals with mutated glucocorticoid receptors who show similar HPAA dysregulation and exhibit increased depressive-like behaviours in response to stress, compared to

wild type mice[83]. More details on the relationship between cortisol and depression are provided in chapter 8.

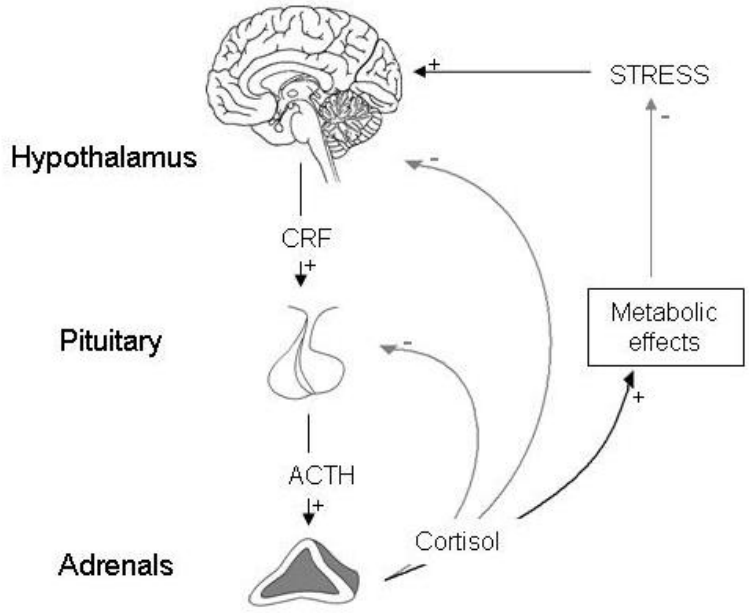


Figure 1.4: The Hypothalamic-pituitary-adrenal axis.

1.2.4.2 Inflammatory Cytokines

Cytokines are small messenger molecules which form part of the immune response. There are over 100 types of cytokines, with multiple and shared functions, but broadly speaking they can be divided into two categories: pro-inflammatory and anti-inflammatory. There is a growing literature on an association between increased cytokines in depression, first proposed by Maes in 1995[84]. Although there is a lot of evidence to support this hypothesis, there remains a great deal of inconsistency in the literature, most likely due to the variety of cytokines and the types of depression being investigated. Basal cytokine levels follow a circadian rhythm, so it is important to consider the time of day[85]. Also, cytokines function through autocrine and paracrine communication and have multiple and shared functions. Many cytokines stimulate the production of themselves and others[86] and as cells are rarely, if ever, exposed to just one

cytokine it is often easier to view them as components of a message. The strongest evidence suggests a link between four inflammatory cytokines and depression. These are: interleukin-6 (IL6), interleukin-1 beta (IL1ß), tumour necrosis factor alpha (TNFα) and interferon gamma (IFNγ). There is also some evidence of an association between C-reactive protein (CRP) and depression[87]. CRP is a non-specific acute phase protein the production of which is stimulated by IL6[88]. CRP is often monitored as part of routine hospital blood tests so could be a quick and easy biomarker.

Evidence of the effects of cytokines on mood has been found through three types of studies: cytokine therapy studies, differences in levels of inflammation in depressed and non-depressed individuals, and neurobiological in vivo and in vitro studies investigating potential mechanisms by which cytokines may induce a change in mood. Although increased cytokines are still not considered suitable for use as a biomarker for depression in the general population[89], two meta-analyses have concluded that there is a significant increase in inflammation in depressed patients[87, 90]. There is also evidence towards the effects of cytokines on mood through cytokine therapy studies[91, 92] and neurobiological in vivo and in vitro studies investigating potential mechanisms by which cytokines may induce a change in mood (e.g. Harrison *et al*., 2009[93] or see Dantzer *et al*., 2008[31]). Also, like cortisol, cytokine levels increase in response to psychological and physical stress[94, 95]. More detail regarding specific cytokines is provided in chapter 8.

1.2.4.3 Cytokines, stress and the HPAA

Several theories have been proposed for the mechanisms underlying the association of cytokines with depression. For instance, studies have shown dysregulation of the neurotransmitters serotonin and noradrenaline in patients with depression when compared to controls[96]. Increased levels of cytokines are associated with increases in noradenaline[96] and decreased levels of the serotonin precursor tryptophan, which is required for the synthesis of serotonin[97, 98]. Whilst

all possible mechanisms are likely to play some role in cytokine induced depression, the most compelling evidence supports a connection between cytokines and the HPAA. Although, initially, research focused on the well founded suppressive effects of the HPA on the immune system, later studies demonstrated a bidirectional relationship: cytokines enhance glucocorticoid release and glucocorticoids inhibit cytokine production[99] (see figure 1.5).

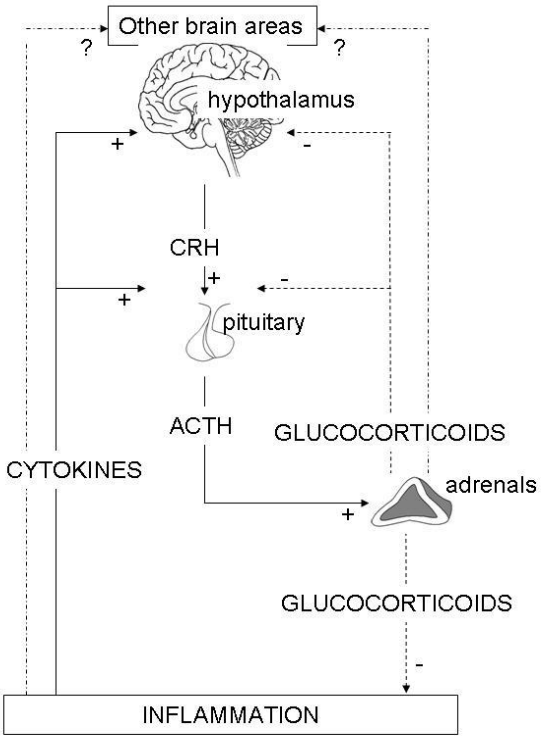


Figure 1.5: Cytokines and the HPAA, adapted from Evans *et al.* (2005)[100].

Like the HPA response, cytokine levels increase in response to psychosocial and physical stress both soon after the stressful event and up to 6 months later[99, 101, 102]. It is now well accepted that cytokines activate the HPAA pathway during physical stress and recent evidence suggests that cytokine regulation of the HPAA also occurs in response to psychological stress[99]. In vivo studies demonstrated increases in ACTH and corticosterone in rats after intravenous injections of IL1,

IL6, TNFα and IFNγ. Zhou *et al*. (1993)[94] also found that an adrenalectomy further increased the post stress IL6 increase usually seen in rats. These findings have also been supported by in vivo work by Pariante and colleagues (1998)[103]. Similarly, in humans intravenous injections of IL6 result in increased ACTH levels one hour after infusion and raised cortisol levels after two hours. Following participants over a longer period of time Mastorakos and colleagues (2006)[104] found that administering IL6 led to increased levels of ACTH and cortisol for seven days, followed by a blunted response. Comparable short term effects have been achieved using much lower doses of these cytokines when infusing intracerebroventricularly, suggesting much of the activation occurs directly in the central nervous system (CNS), supported by the presence of cytokine receptors in the CNS[80]. However, this seemingly refreshingly straight forward story has now been superseded by a more complicated picture suggested by several studies, which will be further elaborated in chapter 9. For instance, labelling techniques suggest that very little of intravenously infused cytokines actually pass through the blood brain barrier, and the intravenous infusions contained high doses of cytokines which suggests that only high doses of cytokines or prolonged lower doses are likely to have a pronounced effect on the HPA though this mechanism[99].

1.2.5 Relationship between psychological and physiological factors

Repeated stress and especially ELS are associated with alterations in the central neurobiological system which leads to dysregulation of the HPAA[82]. Early life stress does not always lead to depression and not all MD patients have suffered ELS, with many other factors influencing the development of depression. Nevertheless, many of the neurobiological effects of ELS resemble those in MD. Those who experienced ELS also show increased cortisol secretion compared to controls[74]. This evidence is supported by similar findings in animal models[105]. Accordingly, retrospective studies by Heim's group (2000)[106] investigating HPAA function in women who were abused in childhood have found greater plasma

ACTH and cortisol responses to laboratory induced acute social stress. However, it is worth noting that more participants in the ELS and MD group in Heim and colleagues' study had comorbid post traumatic stress disorder (PTSD) than those in the MD group. Past work has shown that anxiety and PTSD are also associated with abnormalities in the HPAA[107] and PTSD is also associated with an increased cortisol response to laboratory induced stress[108].

Exposure to stress is far from the only influence on a person's response to a stressor. As one might expect, there is a genetic component to the HPAA response. A twin study showed significant heritability estimates for the mean increase of cortisol and the cortisol awakening response[109] and single genes have been shown to affect the cortisol response to an acute stressor[110]. Also a person's response to a stressor will depend on the type of stress as this will affect their perception and appraisal of the stressor and method of coping[111]. Furthermore, stress reactivity is greatly affected by other recent or current psychosocial or physical stressors and the level of available support[62, 112]. Finally, HPAA abnormalities have also been found in people showing high levels of NE[113-115].

Cytokine levels are also related to other psychosocial risk factors for depression. People with ELS show increased levels of IL6[116] in adulthood as well as an increased cytokine response to infection[117] or social stress[116]. Neuroticism has been shown to be directly associated with IL6 levels in elderly subjects[118], where NE accounted for a large part of the variance in IL6 levels originally attributed to depressive symptoms. Also, coping with the stress of a cancer diagnosis by seeking instrumental social support (e.g. help with shopping or travel to appointments) has been associated with lower levels of cytokines compared to not seeking instrumental social support[119], as have high levels of social attachment[120].

In summary, the likelihood of a person developing depression depends on their genetic predisposition interacting with a combination of early life and ongoing stress. There is also a strong relationship between vulnerability to depression and dysregulation of the HPAA and increased inflammatory mediator levels.

1.3 Cancer and depression

Most people assume that many cancer patients are depressed, probably due to the difficulties that they face, but this view does not take into account the difference between a normal reaction to a life event and a depressive illness; nor the complicated aetiology of depression, the variety of individual responses to being diagnosed with a major illness and the range of cancer treatments and prognoses. This assumption is also largely unsupported by the evidence from the literature and, as is often the case, there is at least one methodological issue which complicates the picture.

Many symptoms of depression overlap with symptoms associated with cancer and sickness behaviour such as fatigue, sleep and appetite problems (see table 1.1). This makes assessing depression in cancer patients more difficult. The problem is avoided in questionnaires and interviews by focusing on mood and cognitions as opposed to somatic symptoms. However, it still needs to be taken into consideration as some questionnaires use more somatic measures than others, which may result in a bias towards high depressive symptoms in cancer patients.

There is also a possibility that people with a past history (PH) of depression are more at risk for cancer because people with depression are more likely to make unhealthy life style choices (see table 1.4). Past research does not support the thesis that depression independently increases the risk of cancer when these factors are taken into account. But there is not enough research on whether the life style factors in depression specifically increase the risk for either CR or HN cancer.

This would therefore select for a population at increased risk of depression after a cancer diagnosis[121].

Depression	HN cancer	CR cancer
Increased alcohol consumption Smoking Obesity	Increased alcohol consumption Smoking	Increased alcohol consumption Obesity

Table 1.4: Lifestyle factors associated with depression and HN, and CR cancer.

1.4 Prevalence of depression in cancer patients

A diagnosis of HN or CR cancer constitutes a major stressor. Most cancer patients experience transient levels of distress but comparatively few develop MD. Studies show that depressive symptoms tend to peak at about three months after diagnosis before returning to pre-cancer levels[122]. Some studies report that depressive symptoms vary according to the site and stage of the cancer, although stage often fails to reach significance[123, 124]. More recently, investigators are suggesting that rates of depression in ambulatory cancer patients are no higher than those of patients in primary care[125].

1.4.1 Colorectal cancer

1.4.1.1 Depressive symptoms

Thirteen studies have used validated questionnaires to measure high levels of depressive symptoms in CR cancer patients (see appendix 1. 1). These studies reported prevalences ranging from 5-37% with an average of about 15%. Two papers that also included a control group found similar levels of depressive symptoms in CR cancer patients to that of the general population[126, 127].

1.4.1.2 Depressive disorder

Only one study investigated DDs using a structured interview[128] and reported that of 98 pre-treatment patients, no patients were suffering from MD. Ashbury *et al*.[129] (2003) reported the number of patients prescribed anti-depressants in a sample of 299 American colon cancer patients. They found 11% of the patients were taking anti-depressants, but point out that anti-depressants may also be prescribed as pain relief and pain medication was associated with anti-depressant use.

1.4.2 Head and neck cancer

1.4.2.1 Depressive symptoms

Comparatively more studies have been carried out on the prevalence of depressive symptoms in HN cancer patients, compared to CR cancer patients. Twenty-eight studies have used validated questionnaires to measure high levels of depressive symptoms in HN cancer patients[121]. These studies found a prevalence ranging from 0.05% to 48% depending on the cancer and timing of the assessment, most reporting levels of 28%. However, Hammerlid and Taft[4] (2001) found no difference in mental health or emotional functioning scores in HN cancer patients compared to the general population by three years after diagnosis.

1.4.2.2 Depressive disorder

Despite a large body of literature on depression in HN cancer, only four studies used a structured clinical interview to measure prevalence of a DD[130-133]. Again, the prevalences found in these studies vary a lot. Kugaya's group found a prevalence of 3.7% and Katz and colleagues found a prevalence of 5% for MD and 15% for minor depression, both of which correspond to the prevalence of depression in the general population of the respective countries[134, 135]. Nevertheless, Morton's group[132] (1984) reported a prevalence of 40% in an earlier

study using DSM III criteria in a small sample of 48 elderly men. However 35% of these patients were undergoing salvage surgery, which as indicated in the treatment section 1.1.2.2 is indicative of poor response to treatment. Also, a more recent study found a prevalence of 27% in 23 pre-treatment cancer patients. However this was a small study in patients with advanced cancer, a large proportion of whom appeared to have a PH of a psychiatric disorder[133].

1.4.3 Conclusions

A large proportion of HN, and some CR cancer patients appear to suffer from high levels of depressive symptoms, with higher levels reported in HN cancer patients. However, despite high levels of depressive symptoms, the prevalence of DDs is lower and close to that of the general population. Unfortunately, there are not enough studies on the prevalence of MD in CR cancer to be able to compare this to the prevalence of MD in HN cancer.

1.5 Consequences of developing comorbid depression and cancer

There are physiological and prognostic consequences of depression in cancer patients. Increased cytokine levels may affect the tumour and depression is associated with poorer treatment outcome. One of the aims of this thesis is to investigate possible relationships between the physiological and prognostic factors.

1.5.1 Cytokines and cancer

Cytokine levels are increased in cancer patients; some tumour cells express cytokines[136] and cancer treatment increases inflammation[137]. Furthermore, the majority of studies that investigated the levels of cytokines in depression and cancer have found a significant difference in IL6 levels in patients with a DD and cancer compared to those with a DD or cancer only, or healthy controls[138-140] and Allen-Mersh and colleagues[141] (1998) found a significant correlation between IL-

2receptor antagonist levels, but not IL6, and HADS scores. However, Kudoh *et al*.[137] (2001) found no difference in IL6 levels in pre operative cancer patients with a DD compared to those without a DD. They also found that the IL6 and IL8 response to surgical trauma was lower in depressed patients compared to controls. Interestingly, all of the studies that found a relationship between depression and IL6 levels studied patients free of psychotropic medication, whereas those that found no difference failed to mention the patients' treatment status.

The full story of the relationship between inflammation and cancer is still under investigation. At present inflammation is often seen as a double edged sword; as although in one sense cytokines activate the immune system, some cytokines are also thought to be involved in tumour progression. It is now accepted that a large part of the tumour micro environment is inflammatory and that cytokines play a major role in tumour progression, but the exact mechanisms and the complex relationships between different cytokines and different tumour cell lines remain largely unresolved[145]. The findings of increased cytokine levels in depressed cancer patients have significant clinical implications, as these patients are not only going to suffer from more of the symptoms of sickness behaviour but some studies have shown IL6 levels to be an independent predictor of cancer survival[142, 143]. A more structured tale of the inflammatory aspect to malignancy is provided in chapter 8.

1.5.2 Quality of life

First and foremost, comorbid depression undoubtedly has a negative impact on patients' QoL[146]. Depression itself is a distressing and debilitating condition, which when dealing with cancer at the same time, is likely to exacerbate the trials that cancer patients must endure. Also, depressed patients are less likely to have access to social support which has been shown to help patients cope with a stressor such as a diagnosis of cancer[147]. There is also evidence towards an effect of depression on symptom reporting[148]. Koller's group[148] (1996) reported

that patients' report of symptoms was more strongly associated with their emotional status at that time compared to that of clinician rated estimates of the QoL based on their physical function.

1.5.3 Mortality

Cancer patients with comorbid depression are already at risk of increased mortality due to the association between depression, poorer overall health and increased all cause mortality. Moreover, depression leads to a number of complications. A meta-analysis found depressed patients show poorer compliance to treatment[149] and poorer adherence to programmes designed to help cut down tobacco use[150]. Also, cancer patients with depression show higher levels of inflammation, which is associated with increased mortality. Taken together, this implies that patients with comorbid depression and cancer may have a higher mortality. Nevertheless, it is unclear whether depression itself increases the risk of cancer mortality, or if depression is a result of poorer prognosis, especially when controlling for all of the other confounding factors.

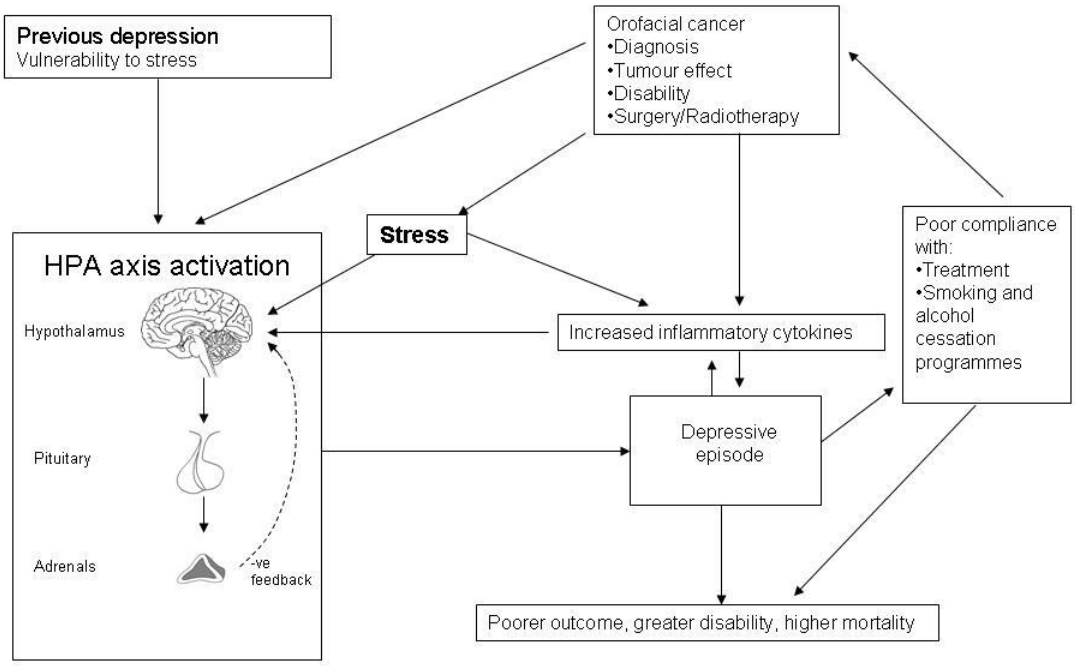


Figure 1.6: Cytokines, HPA, cancer and depression.

1.5.4 Clinical implications

Despite its negative consequences depression continues to be under treated and under diagnosed in cancer patients. Fallowfield and colleagues[6] (2001) reported that less than 30% of patients showing high levels depressive symptoms indicative of a DD were rated as depressed by the clinicians. Keller and colleagues[7] (2004) report higher rates of detection of a DD when compared to DSM-IV diagnosis, but they also report poor specificity - over 50% of those without a disorder were also thought to be depressed by the clinicians. Moreover, only 40% of the patients suffering from a DD were referred to psychological liaison services, despite evidence that comorbid depression and cancer is treatable[151]. Depressive symptom questionnaires can be used to screen for a DD, for instance using a total score of 15 or over on the HADS as indicative of a DD picked up 72% of patients

with a current DD. However reliance on the HADS would mean that clinicians would still miss 28% of patients with a DD and with only 81% specificity almost one in five of DD case level patients according to the HADS score would not have a DD. Given these findings the benefits of using screening instruments as the primary method of identifying patients with depression may not outweigh the costs. This is especially true in busy resource limited cancer clinics. Thus it is perhaps not surprising that screening has not been widely adopted in clinics throughout the UK[125]. One of the aims of this thesis is to explore what factors might increase the risk of developing a DD, including risk factors applicable to general population as well as unique to cancer patients. This is so future patients who are at an increased risk of developing depression can be monitored and provided support to help improve treatment outcome.

1.5.4.1 Studies investigating mortality in cancer patients with comorbid depression

There are no studies that have investigated the impact of depression on cancer mortality in HN, or CR cancer specifically. However there is a reasonably large literature including many other different cancer types. Most studies look at all cause mortality. Four studies used diagnostic criteria to investigate the effect of comorbid depression on cancer mortality[152-155]. Two of these studies found a significant effect of a DD on cancer mortality[152, 155], but only one of these included cancer variables and neither adjusted for smoking or alcohol consumption. Fifteen studies investigated the impact of depressive symptoms on mortality[121] of which nine showed a significant impact on mortality, but again only one of these studies adjusted for cancer stage or smoking. Studies that investigated single measures of depressive symptoms usually found no effect. All of the studies investigating a PH of depression found an increased risk of cancer mortality[152, 153, 155, 156]. No studies found a decreased risk of cancer mortality in patients with comorbid depression.

It is difficult to interpret the results of these studies due to the multiple confounding factors and the extent of variation in different cancers and depression assessments. These results, if purely based on numbers, are, as Evans *et al*[100] (2005) state, “intriguing, but by no means definite” (pp179). There appears to be a trend towards increased mortality in people with a syndromal DD, but few of these studies adjusted for important confounders, which would undoubtedly affect the findings. Also, no studies have investigated just CR or HN cancer, probably due to the numbers that would be required for such an investigation.

1.6 Conclusions

1. Past investigations suggest that although many patients suffer from depressive symptoms (which could be transient) following a diagnosis of cancer, prevalence of MD is closer to that of the general population.
2. Depressive disorders are associated with ELS, ongoing stress, dysregulated stress hormone response and increased inflammation.
3. Inflammation plays a role in the proliferation and invasiveness of malignant tumours. Although the exact role depends on the tumour and cytokine, often cytokines aid tumour progression and proliferation.
4. There is evidence that cancer patients who have comorbid depression are less compliant with treatments and have higher cytokine levels
5. Comorbid depression and cancer lead to poorer QoL, and possibly increased mortality.

There is a lot of research on prevalence of depressive symptoms in cancer patients, but much less on prevalence of DDs. Also, a lot of studies have documented the detrimental impact of comorbid depressive symptoms on QoL in cancer patients, but relatively few have studied the biological impact of depression in cancer patients. Also, those investigating mortality often fail to adjust for key covariates.

There are very few studies using long term assessments and validated diagnostic measures and no prospective studies that also look at possible mechanisms by which cancer and mood may influence each other.

Despite a varied literature on the associations and individual aspects of inflammation in depression and cancer, it is still not clear whether

i) The increased inflammation in patients with comorbid depression results in increased risk of mortality due to the poorer prognosis associated with increased cytokine levels

ii) Poorer prognosis and associated inflammation lead to depression (see figure 1.7).

Or iii) Both of the above.

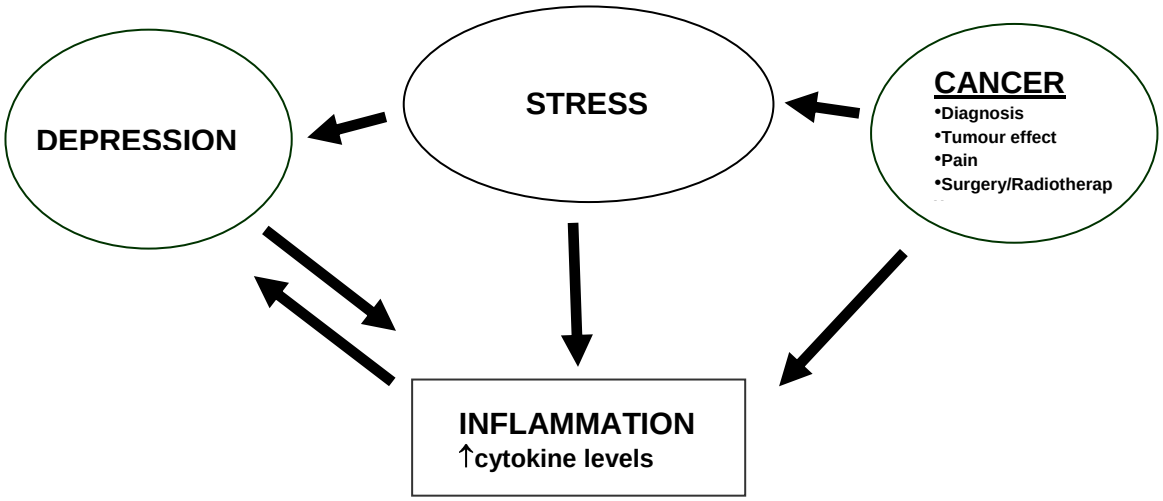


Figure 1.7: Cancer, depression and inflammation.

1.6.1 Aims and Hypotheses

The main aims of this study are to:

1. Measure the prevalence of DDs in two different cancer clinic populations.
2. Test the hypotheses that:
    - (i) Patients with a PH of depression are more likely to experience a DE following a cancer diagnosis.
    - (ii) Depressive symptoms have a significant negative effect on QoL.
    - (iii) Patients with higher cytokine levels show more depressive symptoms.
    - (iv) Patients with increased HPAA activity (increased salivary cortisol levels) show increased depressive symptoms.
    - (v) Patients with increased HPAA activity show increased inflammation (increased cytokine and CRP levels).

As well as the main hypotheses this study explores associations between other possible explanatory factors on depressive symptomatology, inflammation and cortisol dysregulation such as coping styles, personality and patient rated cancer related symptoms.

This thesis investigates some of the major factors in an exploratory manner, as no power calculations are possible. It is acknowledged that some factors, such as genetics, are not considered; including such variables would be beyond the scope of this study even for exploratory purposes. The thesis focuses on psychosocial variables which are associated with stress responses and vulnerability to depression. A conceptual model of hypotheses is shown below (figure 1.8) which is based on previous research described in this chapter. Specific hypotheses and relevant studies are presented in each results chapter.

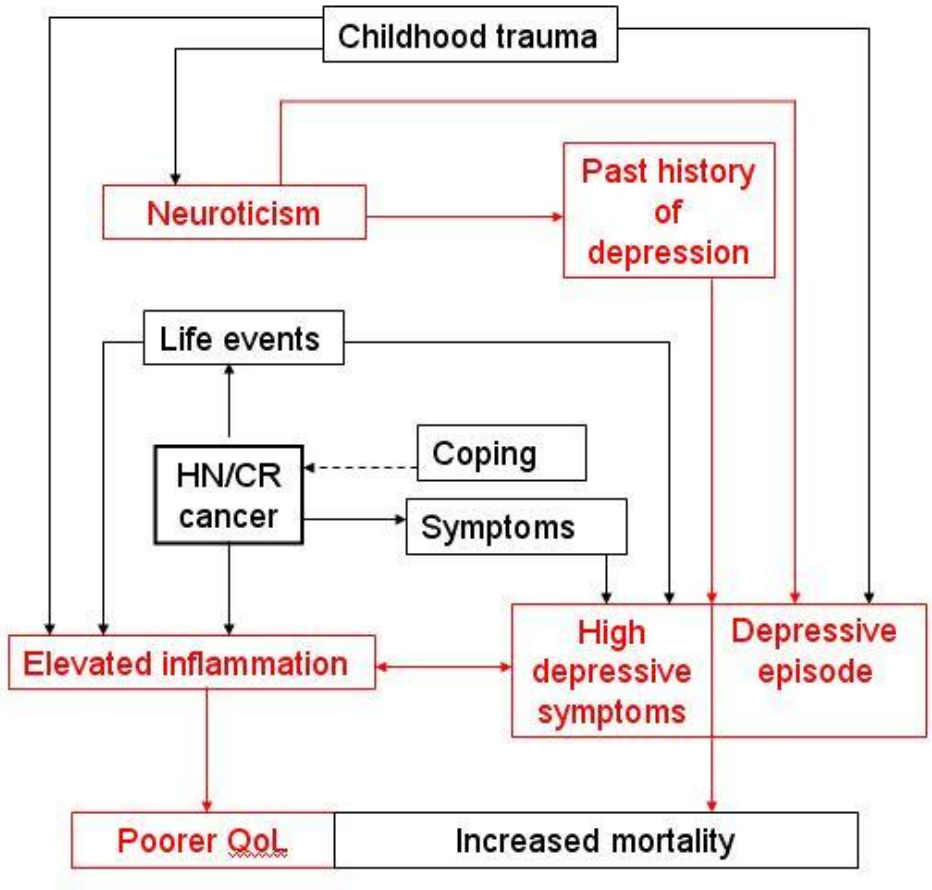


Figure 1.8: Schematic representation of vulnerability for depression after cancer diagnosis.

This work should inform future, larger studies looking at depression and inflammation in cancer patients.

1.6.2 Introduction to design and methods

Two studies were conducted in order to address the aims of this thesis:

The first is a cross sectional study based on all patients attending the HN or CR clinics at St Bartholomew's and The Royal London hospitals for a period of six months. This study investigates depressive symptoms and QoL in HN and CR cancer patients. The major strength of this study is a larger sample size to address the first aim of the thesis.

The second study is a longitudinal investigation on two groups of newly diagnosed patients with HN and CR cancer respectively, who presented to the clinics at St Bartholomew's and The Royal London hospitals between March 2007 and March 2009 and were followed for six months. This study aims to investigate prognostic markers for depression in cancer patients to test the main hypotheses.

2 General Methods

The thesis uses data from two main studies: a prevalence and a prospective study each based at both St Bartholomew's Hospital and The Royal London hospital. This general methods section details the clinics, evaluations and analyses that were used in both studies. Methods specific to each study are explained in the relevant sections: chapter 3 for the cross sectional study and chapter 5 for the prospective study. Both studies were conducted recruiting patients from the same clinics and used the same mood and QoL questionnaires, diagnostic psychiatric interview and regression analysis methods.

2.1 Clinics

The CR patients were recruited from the CR clinic on Thursday mornings at The Royal London Hospital. The majority of clinicians are general surgeons and CR specialists and stoma nurses.

The HN cancer patients were recruited from the HN clinic on Wednesday afternoons at St Bartholomew's Hospital. The HN clinic is run as a multidisciplinary clinic consisting of maxillofacial surgeons, Ear Nose and Throat surgeons, speech therapists, dieticians, oncologists and cancer nurse specialists.

2.2 Evaluations

2.2.1 Hospital anxiety and depression scale

The Hospital and Anxiety Depression Scale (HADS) is a well validated questionnaire designed to assess depressive and anxiety symptoms in hospital patients, therefore the questions relate to non somatic symptoms of depression or anxiety (see appendix 2. 1 for the full questionnaire). The HADS comprises of 14 questions; Spindhoven[157] (1997) report a two factor structure to the HADS with seven questions indicating level of depressive symptoms and seven indicating level of anxiety. Each question has four possible answers rated from zero to three, so that patients' answers can range from 0-21 for each subscale of the questionnaire. Reports suggest that scores of 8-10 on either scale are indicative of a possible anxiety/depressive disorder and scores of greater than 11 suggest a probable anxiety/depressive disorder[58]. Past studies report good performance when used in cancer patient samples, in those with stable disease and free from disease[158]. The HADS is also reported to have high reliability with Cronbach's alpha 0.81 and 0.86 for the anxiety (HADS-A) and depression (HADS-D) subscales (respectively)[159].

2.2.2 European Organisation for Research and Treatment of Cancer

The European Organisation for Research and Treatment for Cancer Quality of Life Questionnaire (EORTC-QLQ)[160] is an integrated system for assessing health related QoL in cancer patients. The core questionnaire has five functional scales, nine symptoms scales and one global QoL measure and is the product of over 10 years of collaborative research (see appendix 2. 2).

The function scales are (number of items):

- Physical function (5)
- Cognitive function (2)
- Role (2)
- Social function (2)
- Emotional function (4)

The symptom scales are:

- Fatigue (3)
- Pain (2)
- Nausea and vomiting (2)
- Dyspnoea (1)
- Insomnia (1)
- Appetite Loss (1)
- Constipation (1)
- Diarrhoea (1)
- Financial difficulties (1)

Past reports suggest good reliability coefficients ranging from .52 to .89 during treatment[160].

For the purposes of this study, the functional scales in this section of the EORTC-QLQ were excluded, as theoretically they could be treated as an outcome as well as a symptom, given that any functional impairment is likely to be related to symptoms and a function related to global QoL. Other studies have used these

measures as outcomes[161] and the functional scales are all reported to have high colinearity with the global QoL measure[162]. Thus, in order to prevent multiple testing for the QoL outcome only the global QoL scale was used in this thesis. The limitations to this method are reported in the final discussion.

The EORTC-QLQ cancer specific modules were also used: CR29 for CR cancer patients and H&N35 for HN cancer patients (see appendix 2. 3 and appendix 2. 4for the CR29 and H&N35 respectively).

The CR29 is still in the final stages of development and currently comprises four functional scales and 13 symptom scales.

The functional scales are (number of items):

- Anxiety (2)
- Body image (3)
- Sexual function (men) (1)
- Sexual function (women) (1)

The symptom scales are:

- Micturition problems (3)
- Defaecation problems (4)
- Abdominal or pelvic pain (3)
- Faecal incontinence (2)
- Bloating (1)
- Dry mouth (1)
- Hair loss (1)
- Trouble with taste (1)
- Sore skin (1)
- Embarrassed by bowel movement (1)
- Stoma related problems (1)
- Impotence (1)
- Dyspareunia (1)

The module has recently shown good validity and reliability for use in CR cancer patients in clinical trials and research[163].

The H&N35 comprises 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality. The module has been tested in Norway, Sweden and The Netherlands, as well as in a large cross-cultural study involving more than 10 countries. It has shown acceptable reliability[164].

The symptom scales are (number of items):

- Pain (4)
- Swallowing difficulties (4)
- Senses problems (2)
- Speech problems (3)
- Problems with social eating (4)
- Problems with social contact (5)
- Less sexuality (2)
- Teeth problems (1)
- Restricted mouth opening (1)
- Dry mouth (1)
- Sticky saliva (1)
- Coughing (1)
- Felt ill (1)
- Taking pain killers (1)
- Taking nutritional supplements (1)
- Using a feeding tube (1)
- Weight loss (1)
- Weight gain (1)

The internal consistency of the scales is good, with past studies demonstrating Cronbach's alpha coefficients of 0.81 (pain), 0.82 (swallowing), 0.72 (senses), 0.74 (speech), 0.87 (social eating), 0.83 (social contact) and 0.95 (sexuality)[165].

2.2.3 Schedules for Clinical Assessment in Neuropsychiatry

Past history of depression or current DE were assessed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview[166]. The SCAN is based on phenomenological descriptions based on the Present State Exam encompassing many symptoms and signs of psychiatric illness. Ratings on the SCAN are based on clinical interview. Clinical vignettes were made for each patient recording their cancer diagnosis and psychiatric history. The semi-structured interview focuses on specific symptoms, which are rated according to their presence, duration and severity. For the purpose of assessing past episodes of depression in these studies, patients were asked to choose their worst past episode and to focus on the worst period of four to six weeks. Participants are taken through the checklist of symptoms and each symptom is rated. A mild symptom is scored as one, a moderate symptom for more than half the period as two and a severe level of the symptom for more than half the period of worst intensity is classed as three. A computer scoring programme (CATEG05) then uses ICD-10 and DSM-IV based algorithms to indicate whether the level of symptoms indicates a psychiatric disorder. Where there was any ambiguity between DSM-IV and ICD-10 a decision was reached by consensus with a psychiatrist using all patient details from the vignettes. Interviews were recorded and a randomly chosen proportion of these were checked for reliability of ratings by two psychiatrists trained in SCAN (Anne Farmer and Ania Korszun).

2.3 Missing data

2.3.1 Items

Single missing items on the HADS and EORTC-QLQ were handled according to the instructions in the HADS and EORTC-QLQ instruction manuals. If only one item was missing on either HADS subscale, the score was calculated by using the mean of other items on the same subscale. Missing items on the EORTC-QLQ were calculated in a similar manner provided that it was a multi-item scale.

Incomplete data in a multi-item scale could be calculated in the EORTC-QLQ by using other items provided that over half of the questions had been answered.

2.3.2 Scales

Multiple imputation was tested for the prevalence data, as it is the preferred method of dealing with the effect of missing data. However, in order to run the imputation, the format of the data needed to be considerably modified so it was considered inappropriate for both samples. Median or mean imputes and sensitivity analyses would also be inappropriate as these methods could easily skew the data, given the high range of scale answers and the relatively small samples. Thus, complete case analyses were considered the most appropriate way to deal with the missing data. There are still disadvantages to complete case analyses such as misrepresentation due to biased samples. However, there were few single missing items in the cross sectional study, except for some more sensitive scales (e.g. sexual function) or those that are inapplicable to many patients (e.g. stoma function). Also, appropriate checks were made for the prospective study; regression analyses were used to investigate biases in participation, based on demographic and baseline data. Further details are provided in the prospective methods in chapter 5. The number of participants included is stated for each analysis.

2.4 Analyses

All EORTC-QLQ scales were treated as continuous. Due to high colinearity, the functional scales on the core EORTC-QLQ were excluded (cognitive function, physical function, social function, emotional function, role function). The item “Felt ill” in the H&N35 was also excluded as it was considered an uninformative measure.

Both studies use regression models for the analyses, which rely on the following assumptions:

1. Independence
2. Normality of residual errors
3. Homoscedasticity

In some cases, it was apparent that the third assumption was not met. Thus 'robust' standard errors were used throughout as these are robust to heteroscedastic error terms (therefore relaxing the rule of homoscedasticity). Using robust standard errors in analyses where the third assumption was met did not change the results.

2.5 Methodological issues

2.6 Self report questionnaires

Self report questionnaires have been criticised because there is a risk that participants answer as they think the experimenter wants them to answer, as opposed to giving their honest answer[167]. This is known as the social desirability effect. Some of the questionnaires used in the prospective study attempt to measure this, in order to estimate the degree to which the participants' answers are due to social desirability. Details of these are provided in the prospective methods in chapter 5.

Self report questionnaires have also been criticised for increased probability of recall bias (as compared to interviews)[168]. This is especially problematic in questionnaires that may be biased by mood (e.g. retrospective stress measures), which may affect the validity of the findings for the prospective study. Also, all of the questionnaires used are therefore affected by the precise timing of the questionnaire, as especially in the case of the HADS the score will be affected by the patients' mood at the time of completion. This may not be truly representative of their mood in the previous few weeks, especially if completing the questionnaire during a clinic visit.

2.7 Participation bias

As with all studies, there is also a risk of participation bias. Although the patients who were not asked to join the study were missed at random, there was no way to investigate differences in those who took part compared to those who declined. Checks were made to investigate differences between participating and non participating patients with the limited data that was available, such as sex and age for the prospective study. Similar checks were conducted to investigate the representativeness of follow up samples using baseline data; potential biases are reported in the results.

PART II

Cross sectional study

3 Cross sectional study

Part 2 of this thesis explores the relationship between depressive symptoms and QoL and point prevalence of DEs in HN and CR patients. The study uses cross sectional data from the HN cancer clinic at St Bartholomew's Hospital and the CR clinic at The Royal London Hospital. The background and methods are described in this chapter. The following chapter reports the results of this study followed by a discussion. The study aims to report:

1. The practicalities of using a screening questionnaire in the respective clinics
2. The prevalence of depressive symptoms and point prevalence of a DE
3. The level of cancer related difficulties reported in the QoL questionnaire
4. Results from some exploratory analyses investigating the relationship between depressive symptoms and QoL

The study was conducted in the same clinics as the prospective study which is described in part 1.

3.1 Background

3.1.1 Prevalence of depression and levels of depressive symptoms

As reported in chapter 2, the prevalence of DDs in both patient groups is expected to be similar to that of the general population (about 10%[59]). Based on the reported literature in Chapter 1, the proportion of patients with high levels of depressive symptoms (over eight on the HADS-D) is expected to be around 15% for CR patients and 25-30% in HN patients.

3.1.2 Variables associated with higher depressive symptoms

Very few studies have investigated the association between physical and depressive symptoms in CR cancer patients. Kurtz and colleagues[169] (2002) found that more physical symptoms, comorbid conditions and being female were all associated with higher depressive symptoms in a sample of 234 older patients. Physical functioning was also highly associated with depressive symptoms. Thus, it is expected that symptoms that interfere with physical function, such as fatigue, will be associated with increased depressive symptoms in CR cancer patients.

Many more studies have been conducted on HN cancer patients, which report comparable findings to those of the CR cancer patients; overall symptoms that interfered with social function were more likely to be associated with depressive symptoms. Pain, disfigurement, social problems, difficulty chewing, swallowing and speaking have all been reported to be associated with depressive symptoms, along with fatigue and lack of appetite, in a heterogeneous group of 68 patients, all at least six months post surgery[56, 170]. Similarly, others have found loss of social function to be associated with reduced life satisfaction in a similar set of 115 patients[171]. Other moderate predictors of poor QoL are: receiving chemotherapy and/or radiotherapy; site and stage of the tumour; time since diagnosis; and tracheotomy[172]. Functionally, speech, swallowing and chewing have a high influence on QoL[52] and patients often report persistent functional problems even

after 12 months. One study found that over 35% of pharyngeal cancer patients still had a lot of difficulty swallowing solid food three years after their diagnosis[146]. Thus, high scores on the pain, fatigue, appetite loss, dysphagia, social eating and social contact scales of the EORTC-QLQ H&N35 are expected to be associated with increased depressive symptoms in HN patients.

3.1.3 Variables associated with poorer quality of life

As with depressive symptoms, relatively few studies have been conducted on QoL using CR cancer patient samples. Two recent reviews[57, 173] on long term QoL in CR cancer patients suggest that CR cancer patients have fewer concerns relative to other cancer patient groups, with fatigue and poorer physical function reported to be the most problematic. Patients with colon cancer are also reported to have fewer symptoms than patients with rectal cancer. However, many patients still report difficulties with defaecation and sexual function: the sexual function problems are more likely in the rectal patients due to lower pelvic resection[173-175]. Both those with and without stomas report problems with diet restrictions, bowel movement, body image and medication dependence[57, 174], though more so in stoma patients than those without a colostomy. Very few studies have used the CR29 due to its recent validation and no studies have looked at associations between CR29 symptoms and overall QoL. However, past studies that have reported on QoL in CR cancer patients have focused on patients who finished treatment over 12 months previously. This study focuses on patients who finished treatment at least six months previously, so in that sense the findings from this study should be comparable to past studies. Thus, defaecation problems, sexual function and body image problems are expected to be the physical symptoms most highly associated with global QoL in CR cancer patients.

Many studies have been conducted on QoL in HN cancer patients. As mentioned in chapter 1, HN cancer patients may have to deal with disfigurement as well as numerous functional difficulties. Most studies report the findings that overall QoL

usually falls soon after diagnosis before returning to baseline 12 months after diagnosis[4, 176-178]. However, the studies also report long term functional impairments that persist, such as pain, disfigurement, poorer social function, difficulty chewing, swallowing, speaking, teeth problems, dry mouth and poor shoulder function[146, 177, 179]. Some have found an improvement throughout radiotherapy[180] whereas others find a decrease in relation to adjuvant radiotherapy over time[178] due to disfigurement, dysphagia and chewing difficulties. Overall, studies indicate that some functional difficulties continue (particularly side effects from radiotherapy), but these do not necessarily translate to poorer self-rated overall QoL, possibly due to psychological adjustment or reduction in the severity of the symptoms over time. Terrell and colleagues[172] (2004) found that a tracheotomy tube and other comorbid conditions were reported to be the most troubling symptoms in HN cancer patients; whereas other researchers have reported pain, swallowing, dry mouth and problems with taste and smell to be the most problematic[146]. Thus, as with depressive symptoms, impairments that interfere with social function are expected to have a high association with overall QoL.

Depression is hypothesised to be strongly associated with QoL in both sets of cancer patients[146, 181].

3.2 Methods

3.2.1 Aim and design

A quantitative cross sectional study was carried out to investigate the association between PH of depression, current depressive symptoms, QoL and DD in HN cancer patients and CR cancer patients. Ethics approval was obtained (Ref: 08/H0701/63) from the local NHS research ethics committee.

3.2.2 Evaluations

The following assessments were used:

Questionnaires:

1. The HADS as described in the evaluations section of chapter 3.

2. The EORTC-QLQ, including the cancer specific modules CR29 and H&N35 as described in the evaluations section of chapter 3.

3. A Past Mental Health Screening Questionnaire (PMHS) (see appendix 3. 1 and appendix 3. 2). This questionnaire asked 5 questions on whether a patient has experienced or been treated for either depression or anxiety:
    i. Have you ever been treated for depression?
    ii. Have you ever been treated for anxiety?
    iii. Have you ever been prescribed anti-depressants?
    iv. Do you think you have ever suffered from depression?
    v. Do you think you have ever suffered from anxiety?

    The questionnaire also asked if the patient would be willing to be contacted by a researcher for an interview.

Finally, a structured diagnostic interview was also used, as follows:

The SCAN as described in chapter 2. This study used an annotated SCAN, which is shorter than the regular version of the SCAN, as used at the Social Genetic and Developmental Psychiatry department at the Institute of Psychiatry (personal communication from Anne Farmer). The ratings from the SCAN interview are entered into a computerised scoring programme CATEGO5 which provides diagnoses according to DSM-IV or ICD-10 operational definitions.

3.2.3 Colorectal methods

3.2.3.1 Procedure

All CR patients attending the clinic on a Thursday morning for a six month period were given the HADS, EORTC-QLQ, and PMHS (once) to be completed whilst they waited for their appointment. The reasons for not completing the questionnaire were noted and are mentioned in the results section in chapter 4.

The treatment team were alerted if a patient had a total score of 15 or above on the HADS.

Patients who scored over seven on either HADS subscale, or answered yes to any of the mental health questions on the past mental health screening questionnaire and who consented to be contacted on the PMHS were called at a time convenient to the patient. This phone call took an average of 20 minutes and was used to give an annotated SCAN interview.

3.2.3.2 Participants

Three hundred and forty patients completed the questionnaire. Seventy-one patients were CR cancer patients, 258 patients were suffering from benign CR related health problems or were undergoing investigations for bowel related symptoms such as blood in stools or change in bowel habit. Eleven patients were suffering from non CR cancers and were excluded from the analyses as there was not enough power to analyse this group as a discrete sample, but they were too different to be combined with either the control or CR cancer patients. Of the 340 patients, 222 provided a telephone number for a SCAN interview. Of those contactable, 78 patients met criteria to be contacted for interview, 64 of whom completed a full interview. Full details of completion are provided in the results section of chapter 4.

Figure 3.1 shows the flowchart of the procedure and patient participation.

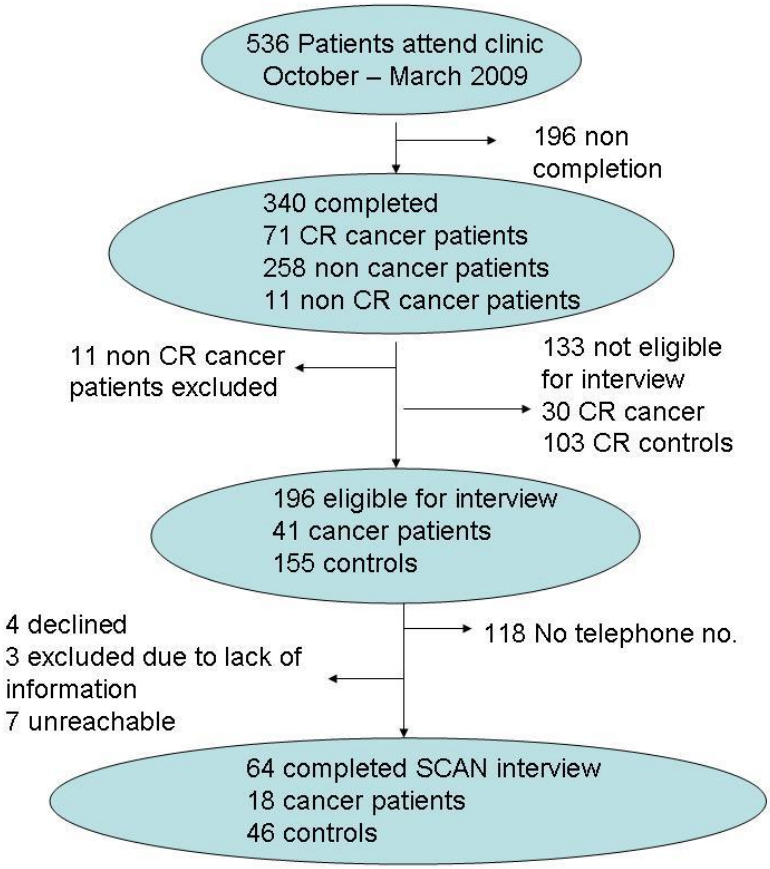


Figure 3.1: Flowchart of the procedure and patient participation in the CR clinic.

3.2.4 Head and neck methods

3.2.4.1 Procedure

In an initial audit, all maxillofacial HN cancer patients attending the HN clinic on a Wednesday afternoon between January and June 2007 were asked to complete the EORTC-QLQ and HADS whilst waiting for their appointment.

All HN cancer patients who completed the HADS and EORTC-QLQ as part of the initial audit were sent the PMHS, HADS, EORTC-QLQ and H&N35 along with a

covering letter and freepost envelope, in January 2009. Patients who had yet to return the questionnaire were sent out one more pack with only the PMHS cover letter and freepost envelope included, in May 2009.

Patients who scored over seven on either HADS subscale, or answered yes to any of the mental health questions on the past mental health screening questionnaire and who consented to be contacted on the PMHS, were called at a time convenient to the patient. This phone call took an average of 20 minutes and was used to give an annotated SCAN interview.

The clinicians were alerted to all patients who scored over 15 on the depression subscale on the HADS.

3.2.4.2 Participants

Two-hundred and thirty seven HN cancer patients completed the HADS and the EORTC-QLQ between January 2007 and July 2007 as part of an initial audit. Two hundred and twenty-five patients were followed up in January 2009 (11 patients had since passed away and three patients had given insufficient information to track their records). Of the 225 patients, 86 returned all three questionnaires and a further 19 completed the PMHS. Thirty-three of those patients met criteria to be contacted and took part in the SCAN interview. Percentage completion and reasons for non completion are reported in the results section in chapter 4.

See figure 3.2 for a consort diagram of the procedure and patient participation.

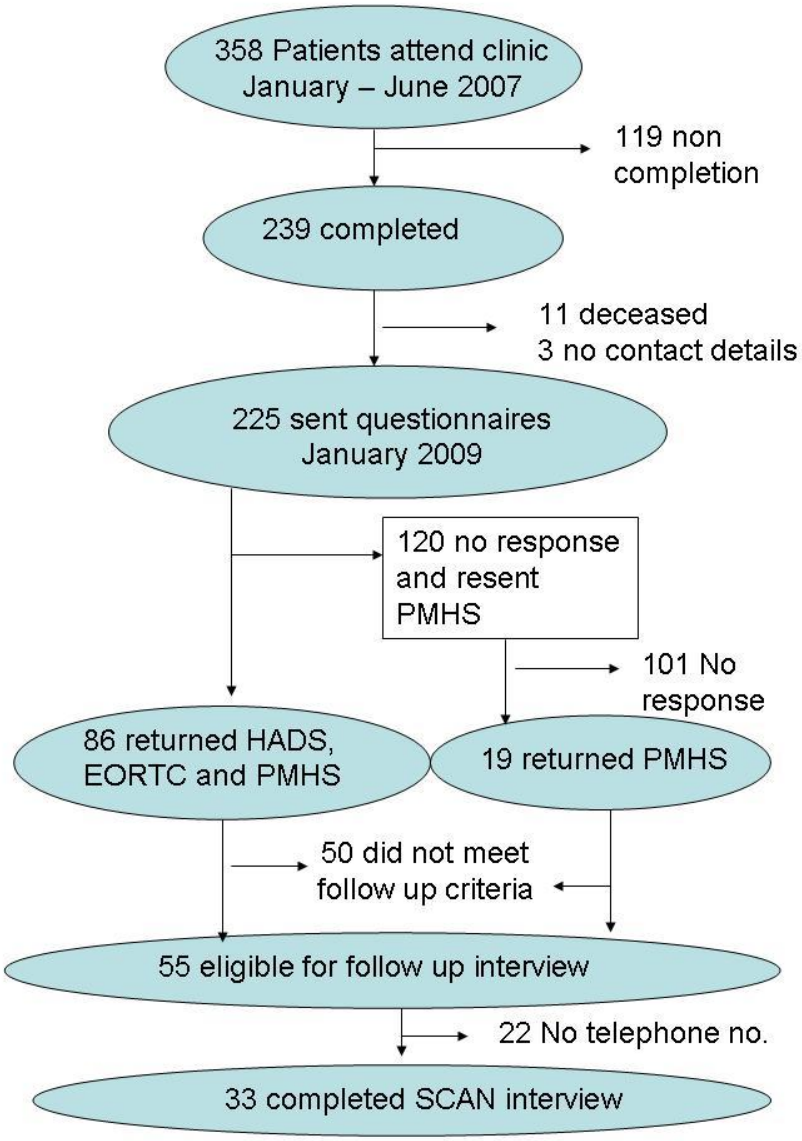


Figure 3.2: Consort diagram of procedure and participation for HN clinic.

3.2.5 Analyses

1. Checks were made for missing data. Item non response is reported in the results section of chapter 4.

2. ANOVAs and Chi square tests were carried out to test for differences and variance in demographics and depression variables between CR controls and cancer patients and CR cancer and HN cancer patients.

3. Regression analyses were carried out to check the representativeness of the patients who returned the questionnaire and agreed to be contacted for an interview compared to those who did not agree to be contacted for an interview.

4. Univariate and multivariate regression analyses were carried out on each patient sample with depressive symptoms, global QoL and current DE as dependent variables. Age, sex, all other QoL measures, HADS scores and PH of depression or anxiety were all used as independent variables in the model.

4 Cross sectional results

This chapter presents the results from the cross sectional study including:

- The practicalities of the screening method
- The prevalence of high levels of depressive symptoms and the percentage of those patients who had a DD
- The chapter also shows the results of an exploratory analysis designed to investigate
    1. The symptoms that were most strongly independently associated with depressive symptoms
    2. The factors most strongly associated with present DE
    3. The symptoms that were independently associated with global QoL

The results are reported in the order presented above, always presenting the results for the CR patients first, followed by the results for the HN patients. The chapter concludes with a discussion of the main findings.

4.1 Practicalities of screening method

4.1.1 Colorectal clinic

Three hundred and forty (63%) patients completed the questionnaires, out of 536 attending the clinic in the six months. Of the 340, 21% were CR cancer patients, which is slightly below the estimated proportion of clinic appointments allocated for cancer patients (30-35%). Unfortunately, no diagnosis is available for those that did not complete the questionnaires so it is not possible to test whether diagnosis affected completion rates. Reasons for non-completion are shown in figure 4.1. A number of patients were not reached during their visit to the clinic, due to limited resources in the clinic (termed unapproached).

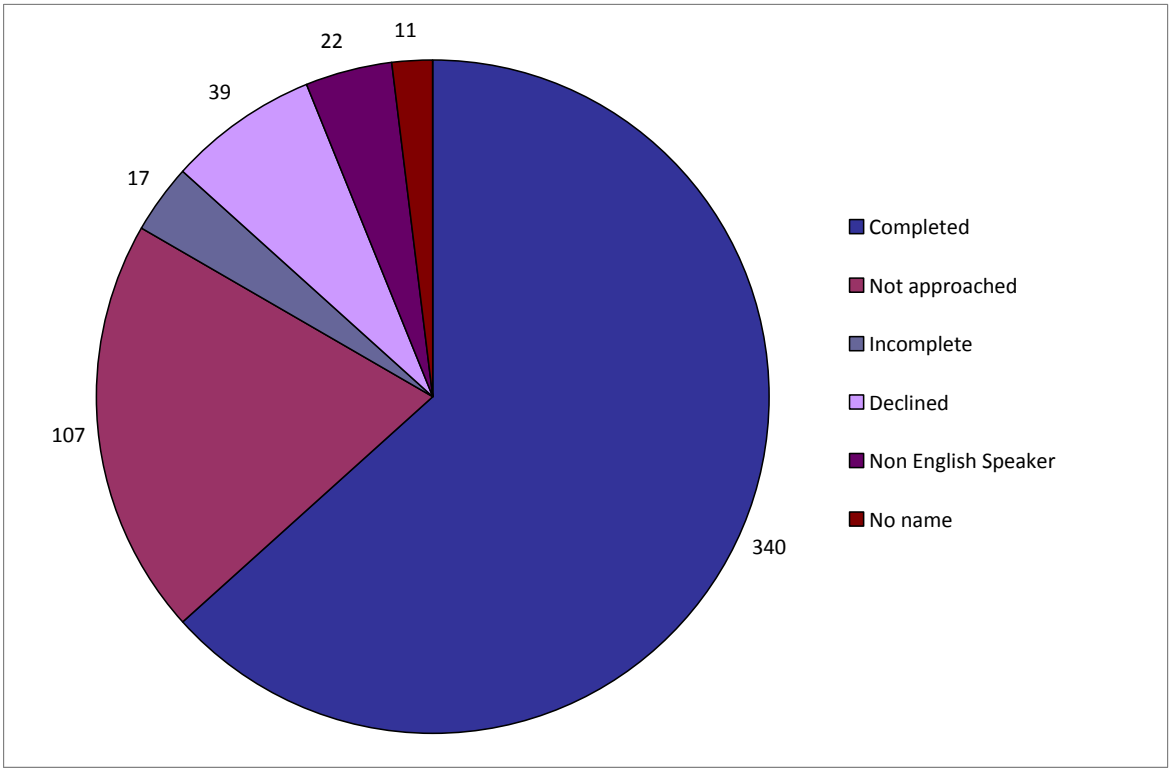


Figure 4.1: Number of patients who completed questionnaire and reasons for non completion in the CR clinic.

4.1.2 Head and neck clinic

67% of the patients attending the clinic completed the questionnaires and only 8% of patients refused (figure 4.2).

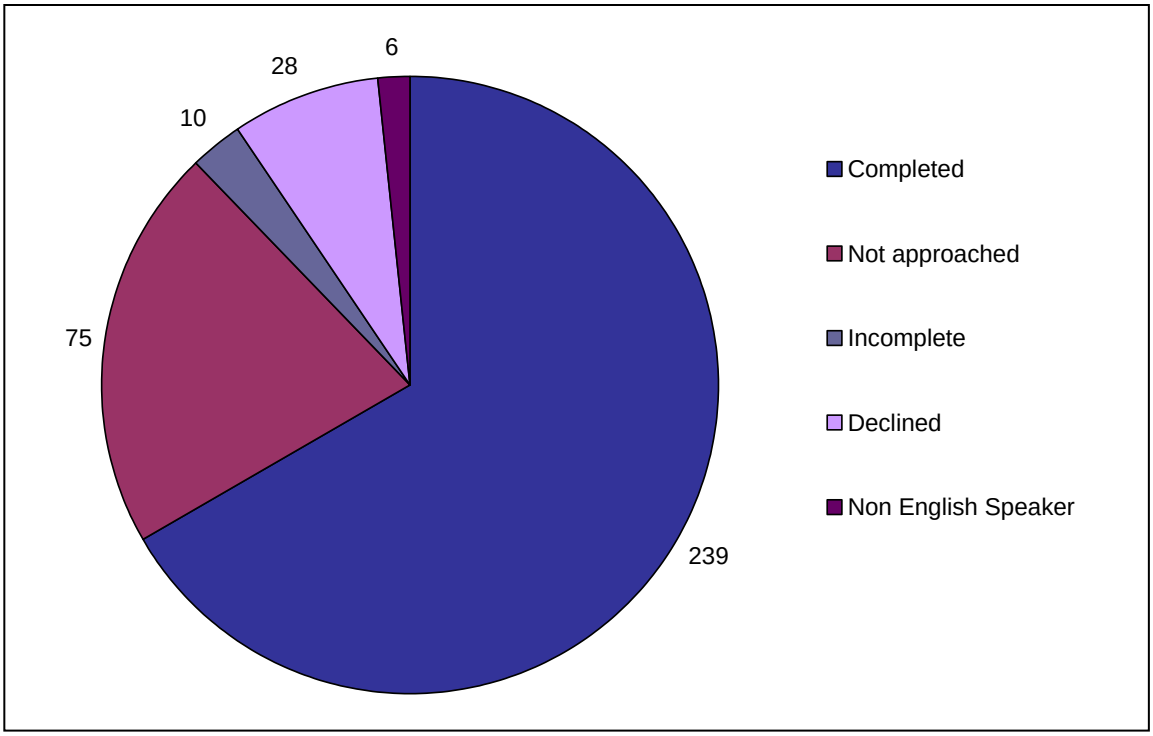


Figure 4.2: Number of patients completing questionnaire and reasons for non completion in the HN clinic.

4.2 Participant information

4.2.1 Colorectal clinic

4.2.1.1 HADS and QoL Descriptives

After calculating incomplete data on multi-item scales, of the 342 completed questionnaires 109 patients had complete data on all sections of the questionnaires. The majority of single missing items (51) were related to sexual function and 258 patients had less than five missing items not including the sexual function items.

Demographic information for the CR cancer and control groups is shown in table 4.1. Colorectal cancer patients were significantly older than the controls. The diagnoses of the non cancer patients are shown in figure 4.3.

		CR controls	CR cancer
Patients		258	71
Age	**Mean (sd)**	**50.79 (16.88)**	**65.50 (13.23)***
Sex N (%)	Female	154 (59.69)	39 (54.93)
	Male	104 (40.31)	32 (45.07)

Table 4.1: Diagnoses and demographic information for all CR patients.*$p<0.0005$

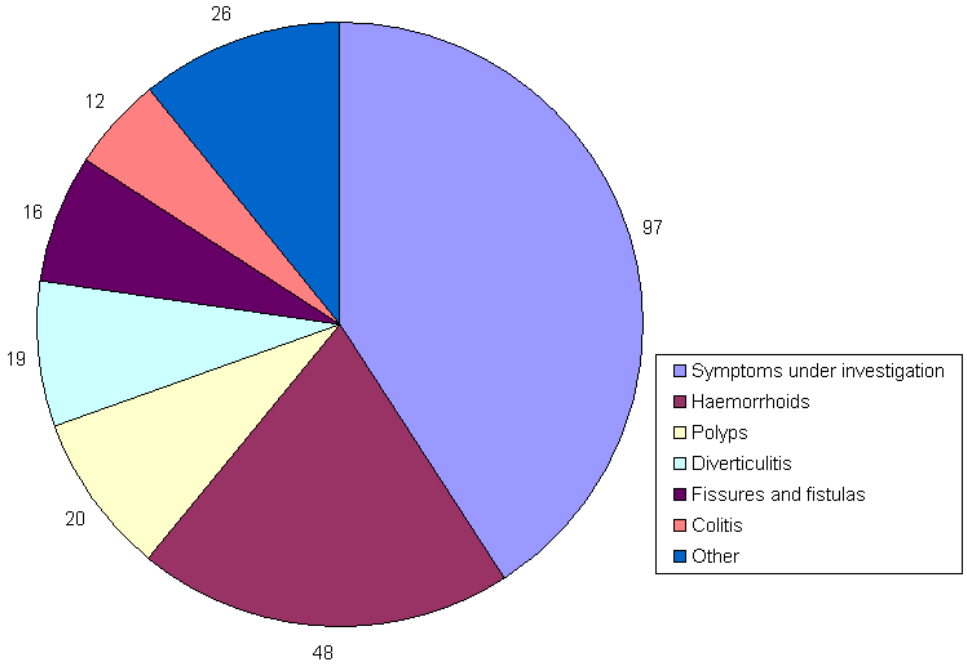


Figure 4.3: Diagnoses of CR control group

There were no significant differences in prevalences of high HADS scores or PH of depression between CR cancer patients and controls (see table 4.2). However, the cancer sample reported higher levels of global QoL overall, which is approaching significance.

		CR control		CR cancer	
	Score	N	(%)	N	(%)
HADS-D	0-7	176	(73.95)	52	(73.24)
	≥ 8	62	(26.05)	19	(26.76)
HADS-A	0-7	134	(56.54)	45	(63.38)
	≥ 8	103	(43.46)	26	(36.62)
>7 on either HADS scale		116	(48.95)	29	(40.85)
Global QoL	**Mean (sd)**	**241**	**59.49 (1.65)**	**67**	**66.17 (3.12)***
Past treatment for depression		59	(22.87)	16	(22.54)
Past treatment for anxiety		28	(10.85)	7	(9.86)
PH of depression		77	(29.84)	20	(28.17)
PH of anxiety		62	(24.03)	15	(21.13)
Any PH		98	(37.98)	26	(36.62)
Any PH or >7 on either HADS scale		155	(60.08)	41	(57.75)

Table 4.2: HADS scores and patient reported past mental health in all CR patients. *$p=0.06$

4.2.1.2 Representativeness

Of the 155 controls patients that were eligible for a follow up interview 58 control patients (37.42%) were happy to be contacted, whereas 20 CR cancer patients (60.61%) were happy to be contacted. Older patients and those presenting to the clinic with a diagnosis of CR cancer were more likely to provide a telephone number. Moreover, those with a self reported PH of depression or anxiety were more likely to provide contact details (see table 4.3).

Baseline characteristic	No contact provided N	(%)*	Contact provided N	(%)*	OR (95% CI)
Gender					
Male	89	(65.44)	47	(34.56)	
Female	128	(66.32)	65	(33.68)	*1.04 (0.65-1.65)*
Diagnosis					
CR control	**181**	**(70.16)**	**77**	**(29.84)**	
CR cancer	**36**	**(50.70)**	**35**	**(49.30)**	***2.29 (1.34-3.91)****
Age Mean (sd)	**217**	**52.62 (17.86)**	**112**	**56.56 (15.74)**	***1.01 (1.00-1.03)****
HADS-D (N=309)					
<7	149	(65.35)	79	(34.65)	
≥8	52	(64.20)	29	(35.80)	*1.05 (0.62-1.79)*
HADS-A (N=308)					
<7	123	(68.72)	56	(31.28)	
≥8	78	(60.72)	51	(39.53)	*1.43 (0.89-2.31)*
>7 on either HADS subscale	91	(45.27)	54	(50.47)	*0.92 (0.50-1.68)*
Global QoL Mean (sd)	202	59.30 (26.46)	106	64.07 (23.94)	*1.01 (1.00-1.02)*
Past treatment for depression	**34**	**(15.67)**	**41**	**(36.61)**	***3.11 (1.83-5.28)****
Past treatment for anxiety	**17**	**(7.83)**	**18**	**(16.07)**	***2.25 (1.11-4.57)****
PH of depression	**44**	**(20.28)**	**53**	**(47.32)**	***3.53 (2.15-5.81)****
PH of anxiety	**39**	**(17.97)**	**38**	**(33.93)**	***2.34 (1.39-3.95)****
Any PH	**12**	**(26.09)**	**32**	**(54.24)**	***3.36 (1.46-7.73)****
Met criteria to be contacted	**114**	**(52.53)**	**82**	**(73.21)**	***2.47 (1.50-4.05)****

Table 4.3: Representativeness of follow up sample in CR clinic. *$p<0.05$

All other QoL measures were non significant (figures not shown) and there was no linear association between HADS scores and likelihood of agreeing to a follow up interview.

4.2.2 Head and neck clinic

4.2.2.1 HADS and QoL Descriptives

Demographics and HADS scores for HN patients at T1 and T2 are shown in table 4.4. Comparison between the scores at T1 and T2 and patient rated past mental health are shown in table 4.5. There was no significant difference between anxiety and depressive categories at the two time points, but the mean depression and

anxiety scores were significantly lower at T2 *[mean HADS-D T1=4.91, T2=3.77 t(321)=2.05, p=0.041; HADS-A T1=5.98, T2=4.27,t(320)=3.06, p=0.002]*.

		T1	T2
Patients		239	105
Age Mean (sd)		58.02 (15.68)	61.36 (12.43)
Sex N (%)	Male	111 (46.44)	46 (43.81)
	Female	128 (53.56)	59 (56.19)

Table 4.4: Demographics of HN patients who completed the questionnaires at each time point.

		HN cancer T1*		HN cancer T2	
	Score	N	(%)	N	(%)
HADS-D	0-7	182	(76.79)	72	(83.72)
	≥8	55	(23.21)	14	(16.28)
HADS-A	0-7	158	(66.67)	64	(75.29)
	≥8	79	(33.33)	21	(24.71)
>7 on either subscale		96	(40.51)	25	(29.41)
Global QoL	Mean (sd)	213	64.26 (25.97)	72	68.29 (24.77)
Past treatment for depression				24	(22.86)
Past treatment for anxiety				11	(10.58)
Taken anti-depressants				21	(20.19)
PH of depression				38	(36.89)
PH of anxiety				32	(30.77)
Any PH				44	(41.90)
Any PH or >7 on either HADS scale				52	(49.52)

Table 4.5: HADS scores and past mental health answers in HN cancer patients. * These figures include the entire sample at T1, but figures are comparable when testing only those in the follow up sample.

4.2.2.2 Representativeness

To find out if the sample at T2 was representative of the clinical sample, regression analyses were carried out, to see whether any baseline characteristics were associated with patient response. As can be seen in table 4.6 response rate was unrelated to most baseline characteristics, apart from age, with older patients more likely to respond.

Baseline characteristic		No response N	(%)	Response N	(%)	OR (95% CI)
Gender						
Male		61	(50.83)	59	(49.17)	
Female		59	(56.19)	46	(43.81)	*1.24 (0.73-2.10)*
Age	**Mean (sd)**	**119**	**53.21 (16.04)**	**105**	**61.04 (12.79)**	***1.04 (1.02-1.06)****
HADS-D T1						
<7		93	(53.14)	82	(46.86)	
≥8		27	(55.10)	22	(44.90)	*0.92 (0.49-1.75)*
HADS-A T1						
<7		86	(56.95)	65	(43.05)	
≥8		34	(46.58)	39	(53.42)	*1.52 (0.87-2.66)*
Global QoL	Mean (sd)	109	64.71 (23.24)	93	66.76 (26.31)	*1.00 (0.99-1.01)*

Table 4.6: Baseline characteristics of those who responded to mail out follow up compared to those that did not in HN cancer patients. **p<0.05.*

As the follow up sample was relatively representative of the sample at T1, analyses were carried out using the sample at T2 which provided more information. More regression analyses were carried out to see which characteristics were associated with providing a telephone number. As can be seen in table 4.7 older patients, with lower HADS-D scores and increased QoL at T1 and those that had a PH of depression or anxiety were more likely to return the questionnaire and give a contact number for an interview.

Baseline characteristic		No contact provided* N	(%)	Contact provided N	(%)	OR (95% CI)
Gender						
Male		97	(75.78)	31	(24.22)	
Female		83	(74.77)	28	(25.23)	*0.95 (0.53-1.71)*
Age	**Mean (sd)**	**178**	**56.11 (16.19)**	**59**	**62.15 (9.98)**	***1.03 (1.01-1.05)****
HADS-D T1						
<7		132	(72.53)	50	(27.47)	
≥8		46	(83.64)	9	(16.36)	*0.52 (0.24-1.13)*$^{\text{Ŧ}}$
HADS-A T1						
<7		119	(75.32)	39	(24.68)	
≥8		59	(74.68)	20	(25.32)	*1.03 (0.55-1.93)*
HADS-D T2						
<7		30	(41.67)	42	(58.33)	
≥8		9	(64.29)	5	(35.71)	*0.40 (0.12-1.30)*
HADS-A T2						
<7		27	(42.19)	37	(57.81)	
≥8		11	(52.38)	10	(47.62)	*0.66 (0.25-1.78)*
>7 on either HADS subscale		73	(41.01)	23	(38.98)	*0.92 (0.50-1.68)*
Global QoL T1	**Mean (sd)**	**160**	**62.11 (25.97)**	**53**	**70.75 (25.09)**	***1.01 (1.00-1.03)****
Global QoL T2	**Mean (sd)**	**62**	**61.98 (52.74)**	**42**	**73.33 (23.05)**	***1.02 (1.00-1.04)*** **
Past treatment for depression		**6**	**(1.04)**	**18**	**(30.51)**	***2.93 (1.05-8.13)****
Past treatment for anxiety		4	(8.70)	7	(12.07)	*1.44 (0.39-5.26)*
Prescribed anti-depressants		6	(13.04)	15	(25.86)	*2.33 (0.82-6.58)*
PH of depression		11	(24.44)	27	(46.55)	*2.69 (1.15-6.32)*
PH of anxiety		10	(22.22)	22	(37.29)	*2.08 (0.86-5.01)*
Any PH		**12**	**(26.09)**	**32**	**(54.24)**	***3.36 (1.46-7.73)****
Met criteria to be contacted		**19**	**(41.30)**	**33**	**(55.93)**	***2.40 (1.30-4.41)****

Table 4.7: Comparison of baseline characteristics of patients who gave their telephone number compared to those that did not in HN cancer patients. * p<0.05, ** p=0.056, Ŧ p=0.10

4.3 Prevalence of depressive disorder

The estimated prevalence of a DD in the clinics is shown in figure 4.1. There were no significant differences between the different diagnoses $[\chi^2(2)=3.31, p=0.191]$.

4.3.1 Colorectal clinic

Of the 192 CR patients who met criteria to be contacted 82 patients gave their telephone number. Of the 82 patients, 78 patients were contacted, of whom 63 completed enough of the interview for a diagnosis (four declined, three were

excluded due to lack of information and seven were unreachable). Figure 4.4 shows the number of patients who met contact criteria, were contacted and provides an estimated prevalence of mental health diagnoses in CR cancer patients and controls. However, although there were no significant differences in those who met criteria to be contacted, cancer patients were more likely to agree to a follow up compared to the number of controls who met criteria for a follow up interview *[N=392, OR(CI)=2.36 (1.13 -4.82) p=0.001]*.

4.3.2 Head and neck clinic

As shown in figure 4.4 only 5% of those willing to be contacted met criteria for follow up and were currently suffering from a DE, whereas almost 30% had suffered a past DE.

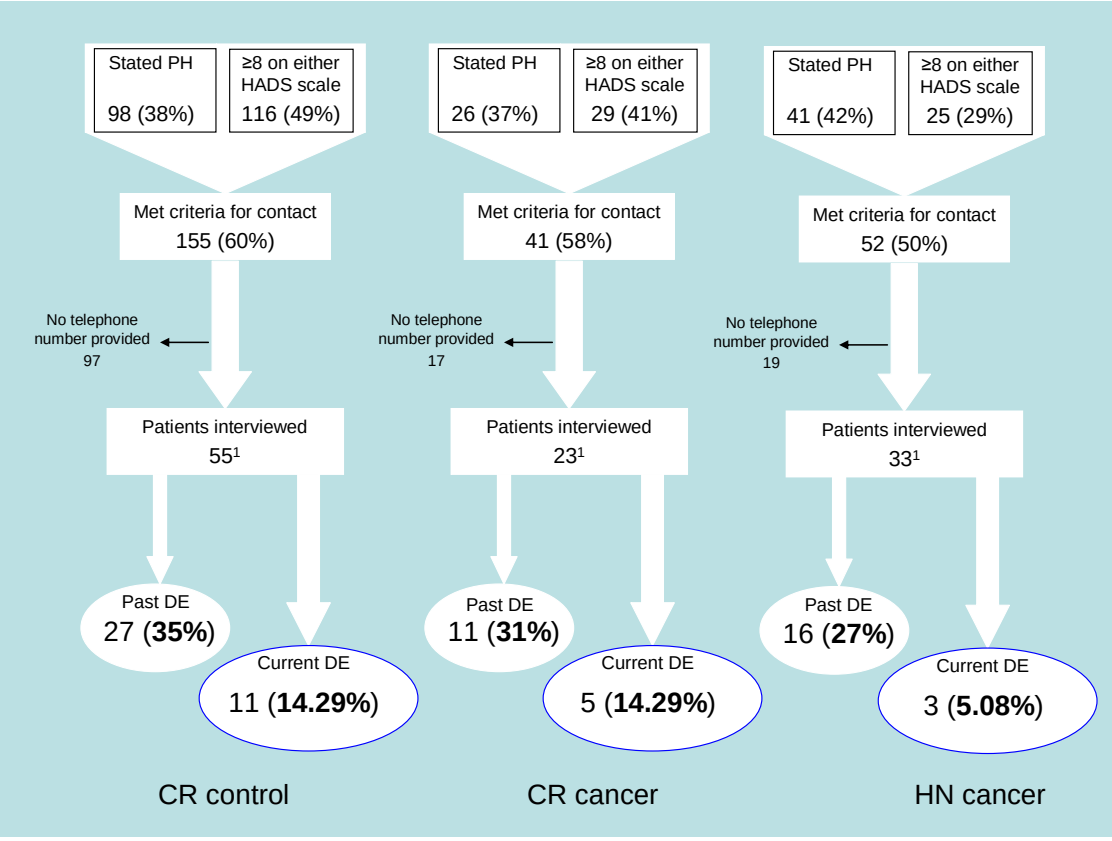


Figure 4.4: Consort diagram of those patients who underwent SCAN interview for diagnosis of DD. 1, some patients were not contactable or did not provide enough information for a diagnosis (see text). Percentages are given as number of patients with PH depression or current DE out of those that were willing to be contacted. Number of patients willing to be contacted is: CR control, 77, CR cancer, 35, HN cancer, 59.

4.3.3 Comparison of depressive symptoms and depressive disorder in head and neck and colorectal cancer patients

Comparison of the screening success and depressive symptoms from cancer patients attending the HN and CR clinic indicate similar patterns of depressive symptoms in the two cancer populations (see figure 4.5 and table 4.8). There was no significant difference in the proportion of patients with high HADS-D scores (scoring ≥8) *[N=308, p=0.129]*. There was no significant difference in the mean HADS-D or QoL score *[HADS-D, p=0.863, QoL, p=0.599]*.

	CR cancer		T1 HN cancer	
	N	Mean (sd)	N	Mean (sd)
HADS-D	71	4.80 (4.16)	237	4.91 (4.42)
HADS-A	71	6.33 (5.48)	237	5.98 (4.49)

Table 4.8: Mean HADS-D scores by cancer diagnosis

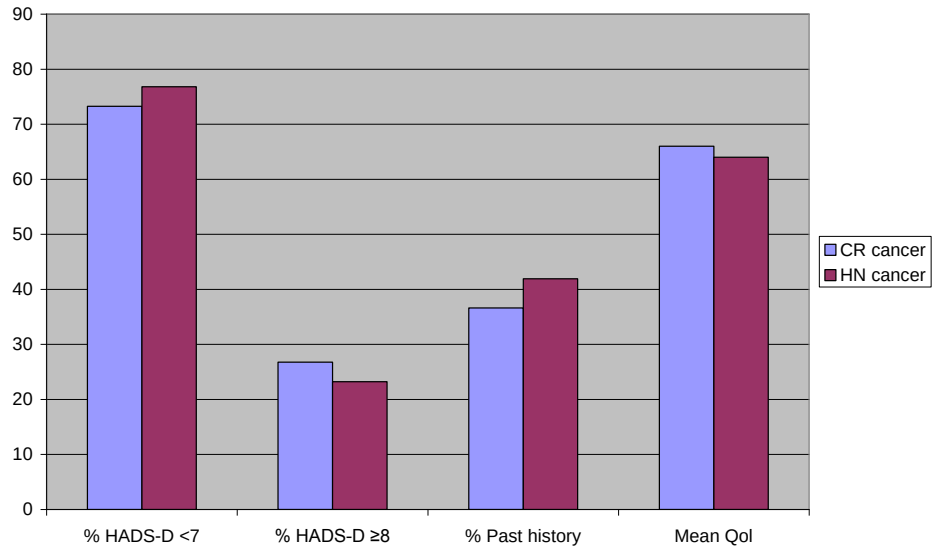


Figure 4.5: Graph showing percentage of patients in each HADS-D category, mean QoL scores and percentage of patients who responded yes to any of the past mental health screener questionnaires. (HADS-D and QoL scores based on T1 data, PH based on T2 data in HN cancer patients.)

4.4 Quality of life descriptives

Descriptives for the QoL scores on the core EORTC-QLQ are presented in table 4.9. There are no significant differences between CR cancer patients compared to non cancer CR patients. Colorectal cancer patients suffered from significantly higher levels of insomnia compared to HN cancer patients at T1. Also, CR cancer patients reported higher levels of diarrhoea compared to HN cancer patients at either time point.

Descriptives for the CR29 module for CR cancer patients are presented in table 4.10. Colorectal cancer patients reported significantly higher levels of micturition problems, hair loss, problems with taste and impotence compared to the control group. However, the control group reported higher levels of abdominal and/or pelvic pain.

Descriptives for the HN specific EORTC-QLQ measures are presented in table 4.11.

Mean (sd)	CR				HN				Difference between CR and HN	
	Control		Cancer		T1		T2			
	N		N		N		N		HN T1	HN T2
Global QoL	241	59.49 (25.59)	67	66.17 (25.54)	213	64.26 (25.97)	72	68.29 (24.77)		
Fatigue	243	39.16 (28.38)	66	36.53 (32.03)	218	35.70 (29.49)	73	32.88 (30.33)		
Nausea and vomiting	244	13.73 (22.36)	67	10.15 (21.48)	216	9.49 (18.64)	73	5.93 (11.90)		
Pain	244	37.09 (33.96)	66	28.68 (30.80)	218	28.98 (33.32)	74	22.07 (31.10)		
Dyspnoea	236	18.64 (29.02)	64	23.44 (31.81)	221	20.97 (29.09)	72	24.07 (31.76)		
Insomnia	242	39.39 (37.07)	**66**	**41.92 (37.58)**	**217**	**30.49 (35.19)**	73	31.96 (33.99)	*	
Appetite loss	236	22.74 (30.22)	66	22.67 (32.11)	210	23.97 (32.31)	72	25.00 (34.37)		
Constipation	239	23.29 (32.07)	66	20.20 (31.42)	214	19.16 (31.01	72	12.96 (24.74)		
Diarrhoea	242	22.72 (32.60)	**66**	**20.20 (34.03)**	**216**	**6.33 (17.49)**	**73**	**5.48 (14.71)**	*	*
Financial difficulties	241	18.81 (32.15)	65	23.59 (35.22)	217	24.12 (33.90)	74	17.12 (23.60)		

Table 4.9: Descriptives for core EORTC-QLQ symptoms. *=p<0.05

Mean (sd)	Control		Cancer		Sig
	N		N		
Health anxiety[Ŧ]	222	61.26 (28.99)	57	61.11 (28.58)	
Body image[Ŧ]	215	77.93 (27.56)	55	79.19 (28.58)	
Function					
Sexual function[Ŧ]	181	62.98 (32.37)	42	69.84 (35.92)	
Micturition problems	**223**	**28.03 (22.78)**	**57**	**35.09 (26.29)**	*
Abdominal/pelvic pain	**223**	**19.36 (21.02)**	**57**	**12.96 (19.68)**	*
Defaecation problems	215	19.37 (21.99)	57	15.45 (23.76)	
Faecal incontinence	151	22.30 (24.79)	48	29.86 (30.93)	
Bloating	217	33.03 (34.84)	58	25.86 (35.89)	
Dry mouth	220	26.06 (28.80)	56	32.14 (33.61)	
Hair loss	**217**	**3.84 (14.00)**	**54**	**10.49 (22.27)**	*
Taste problems	**218**	**9.17 (20.17)**	**55**	**20.00 (29.12)**	*
Sore skin	148	21.97 (32.03)	45	20.00 (34.38)	
Embarrassment	147	24.49 (33.86)	44	20.45 (33.11)	
Stoma problems	14	19.05 (31.25)	7	14.29 (17.82)	
Impotence	**79**	**22.36 (31.45)**	**23**	**42.03 (47.37)**	*
Dyspareunia	84	23.41 (35.01)	12	11.11 (21.71)	

Table 4.10: Descriptives for EORTC-QLQ CR29 for CR cancer patients and controls. **p<0.05*

Mean (sd)	T2 N	
HN pain	74	18.09 (21.96)
Swallowing difficulties	74	21.21 (29.69)
Problems with taste and smell	74	21.40 (29.39)
Speech problems	73	26.64 (27.15)
Problems with social eating	71	33.06 (36.34)
Problems with social contact	73	19.82 (24.45)
Less sexuality	62	46.51 (38.66)
Problems with teeth	73	30.59 (39.58)
Restricted mouth opening	74	32.88 (35.97)
Dry mouth	74	37.39 (35.97)
Sticky saliva	73	35.16 (39.63)
Coughing	74	29.73 (30.00)
Taking pain killers	72	37.50 (48.75)
On nutritional supplements	72	23.61 (42.62)
Presence of feeding tube	73	8.22 (27.66)
Weight loss	73	19.18 (37.64)
Weight gain	72	31.94 (46.95)

Table 4.11: Descriptives for EORTC-QLQ H&N35 at T2.

4.5 Regression analyses

4.5.1 Factors associated with HADS-D

4.5.1.1 Colorectal cancer patients

- Multivariate regression analyses show that only fatigue, defaecation problems and body image were independently significantly associated with HADS-D (see table 4.12).

- All of the symptoms on the EORTC-QLQ (including the CR29) were significantly associated with HADS-D in CR cancer patients in univariate analyses, apart from impotence and dyspareunia.
- Age and sex were not associated with HADS-D.
- None of the PH depression variables were associated with HADS-D.
- Adjusting for age or sex did not change the results.

Independent Variables	N	ß (CI)	P value	Adjusted R^2
Fatigue	*55*	*0.06 (0.03 to 0.10)*	*<0.0005*	*0.65*
Defaecation problems		*0.07 (0.03 to 0.11)*	*0.001*	
Body image		*-0.04 (-0.07 to -0.01)*	*0.021*	

Table 4.12: Regression model showing factors associated with HADS-D in CR cancer patients.

4.5.1.2 Head and neck clinic

The analyses for the HN clinic sample were only conducted using the second set of data as less information is available from the T1 sample.

- The multivariate analyses showed that only fatigue and problems with social contact were significantly independently associated with HADS-D at T2 (see table 4.13).

- All of the EORTC-QLQ symptoms were associated with increased depressive symptoms except for presence of feeding tube, nutritional supplements and weight gain.
- Similar to the CR findings, age, sex and PH depression were not associated with depressive symptoms.
- Adjusting for age or sex did not change the model.
- HADS-D at T1 was significantly associated with HADS-D at T2 in the multivariate model and did not affect the associations between fatigue and social contact problems (from the EORTC-QLQ H&N35) and T2 HADS-D.

Independent Variables	N	ß value (CI)	P value	Adjusted R^2
Fatigue	*65*	*0.08 (0.05 to 0.10)*	*<0.0005*	*0.73*
Social contact problems		*0.08 (0.04 to 0.12)*	*<0.0005*	

Table 4.13: Regression model showing factors associated with HADS-D in HN cancer patients.

4.5.2 Factors associated with global QoL

4.5.2.1 Colorectal clinic

HADS-D, problems with taste, dry mouth and sore skin were the only variables independently associated with poorer QoL (see table 4.14).

- All EORTC-QLQ symptoms were univariately associated with poorer QoL in CR patients except for dyspareunia and impotence.
- As with the results in HADS-D age and sex were not associated with QoL.
- Stoma problems were associated with poorer QoL, but this variable was not included in the multivariate analyses as only 7 patients completed this item.
- Adding age or sex to the model did not change the model.

Independent Variables	N	ß value (CI)	P value	Adjusted R^2
HADS-D	*42*	*-2.37 (-3.42 to -1.32)*	*<0.0005*	*0.77*
Taste problems		*-0.18 (-0.29 to -0.07)*	*0.003*	
Dry mouth		*-0.20 (-0.33 to -0.08)*	*0.003*	
Sore skin		*-0.15 (-0.30 to -0.01)*	*0.039*	

Table 4.14: Regression model showing factors associated with global QoL in CR cancer patients.

4.5.2.2 Head and neck clinic

Only fatigue, problems with social contact, pain and age were independently associated with QoL (see table 4.15).

- All of the EORTC-QLQ symptoms were univariately associated with poorer QoL except from being on nutritional supplements, diarrhoea, weight loss, problems with taste or smell, presence of feeding tube and weight gain.
- Sex was not associated with QoL and age was positively associated with global QoL ratings.
- Adding sex to the model confounded the relationship between age and QoL.
- T1 HADS-D and global QoL did not change the model and were not significantly associated with QoL at T2.

Independent Variables	N	ß value (CI)	P value	Adjusted R^2
Fatigue	*70*	*-0.26 (-0.97 to -0.05)*	*0.018*	*0.70*
Problems with social contact		*-0.38 (-0.57 to -0.19)*	*<0.0005*	
Pain		*-0.20 (-0.38 to -0.02)*	*0.029*	
Age		*0.31 (0.01 to 0.60)*	*0.040*	

Table 4.15: Regression model showing factors associated with global QoL in HN cancer patients.

4.5.3 Factors associated with a current depressive episode

4.5.3.1 Colorectal clinic

No QoL variables, demographics or HADS scales were associated with current DE when analysing just the CR cancer patients. HADS-D was associated with a DE when treated as a categorical variable (over 8) *[N=19, ß(CI)=2.97 (0.19 to 5.75), p=0.036]*.

A second analysis was run that included all the CR patients. In this model only HADS-D and SCAN rated PH depression were independently associated with a current DE (see model 1 table 4.17).

Univariate associations
Financial difficulties (61)
HADS-D (63)
SCAN rated PH depression (65)
HADS-A (63)
Body image* (53)
Patient reported PH depression (65)
Past treatment for depression (65)
Increasing age* (65)
Insomnia (63)

Table 4.16: Univariate associations for current DE in CR patients. Variables are in order of R^2.* negative association

- Table 4.16 shows the variables univariately associated with a current DE in CR patients.

- All of the associated variables increased the risk of a DE except for body image function in which better body image function was protective against a DE and age where increasing age was protective.
- Adding sex or age did not affect the model.

As the SCAN rated PH depression is unlikely to be a practical assessment in a cancer clinic another model was run excluding SCAN PH depression. In this model only body image function was significantly independently associated with a current DD (model 2, table 4.17), although fewer patients completed that item on the questionnaire. Age, sex and diagnosis were not significant in the model and did not affect the presented associations.

Model	Independent Variables	N	OR (CI)	P value	R^2
1	*HADS-D* *SCAN PH depression*	*63*	*6.49 (1.23- 34.06)* *1.31 (1.07-1.61)*	*0.011* *0.024*	*0.31*
2	*Body image*	*53*	*0.97 (0.94-1.00)*	*0.024*	*0.12*

Table 4.17: Regression models showing factors associated with current DE in all CR patients and only CR cancer patients.

Body image was also significantly associated with a SCAN rated PH of depression *[N=53, ß(CI)=-18.20 (-32.77 to -3.63) p=0.015]*.

4.5.3.2 Head and neck clinic

Only three people out of those interviewed for a DD were suffering from a current DE, so no further analyses were carried out with current DD as a dependent variable as there would not be sufficient power.

4.6 Summary

About two thirds of patients completed the questionnaires in both clinics, but many patients were missed due to limited resources.

There were very few differences in the CR cancer patients compared to the CR controls, except that the cancer patients were older and had higher ratings of QoL. The CR cancer patients were also more likely to agree to a follow up interview compared to non cancer patients.

Younger HN cancer patients were more likely to return the mailed out questionnaires and they were more likely to agree to a follow up interview if they had a PH of depression. This was also true of the CR patients.

The levels of depressive symptoms were similar in the CR and HN cancer patients (means of 4.80 and 4.42 respectively, with 27% CR cancer patients and 16-23% of HN patients having HADS-D scores indicative of a possible DE). Although it was hoped that comparisons could be made between the CR cancer patients and the HN patients for prevalence of a DE, this is unlikely to be reliable due to the biases in the followed up HN sample, therefore the prevalence of depression in the HN population is probably much lower than the true prevalence in the clinic.

The multivariate analyses showed that only fatigue and symptoms specific to the cancer site were independently associated with increased depressive symptoms (defaecation and body image function in CR cancer patients and problems with social contact in HN cancer patients). However, HADS-D was only independently associated with poorer QoL in CR cancer patients, along with taste problems, dry mouth and sore skin. The former symptoms of which are likely to be related to chemotherapy treatment. In HN cancer patients the cancer symptoms associated with HADS-D; fatigue and problems with social contact appear to have a stronger association with poorer QoL then HADS-D alone, along with pain and age. This

may be because even though there was no difference in HADS-D scores at the time of the interviews the HN sample was biased towards patients with lower HADS-D levels at T1 and better QoL at T1 and T2.

Multivariate analyses on factors associated with current DE could only be carried out on CR patients due to low numbers in the HN cancer group. Not surprisingly, HADS-D and SCAN rated PH depression were the only variables independently associated with a current DE. Another second model was tested which excluded the SCAN rated PH depression from the model because the SCAN rated PH depression would not be a practical indication of risk of a DE in a busy clinic. In this model only poor body image function (i.e. lack of confidence in body image) was significantly associated with a DE (and HADS-D was no longer significant – due to the association between HADS-D and body image). This finding could be expected given SCAN rated PH depression was also associated with poorer body image function.

4.7 Discussion

4.7.1 Prevalence of depression

The response rate for the questionnaires was relatively good and the refusal rate was low. The mean HADS-D scores were similar in each diagnosis and slightly higher than the mean HADS-D scores in the general population at all ages (3.68)[182], and close to the mean in those over 65 years old (4.6)[183]. The prevalence of high depressive symptoms was slightly higher in the CR cancer group then most studies report, though still well within the range of past studies and not much above the range of general practice patients[2] (18.5% (16.5-20.6%)[184]. Conversely the prevalence of high depressive symptoms in the HN cancer patients was lower than in previous reports, though again still within the expected range. Despite a slightly lower prevalence in the HN clinic this was not

[2] From a sample of >1500 Norwegian patients

significant and there were no significant differences with regard to HADS scores between the two groups, or the CR control group. This finding conflicts with previous reviews on depression in cancer patients which suggest that HN patients would have higher levels of depressive symptoms then CR patients[185], but a comparative study of psychological distress by cancer site found little difference between the two groups[186]. However, both findings were within the expected range and depressive symptoms only give a snapshot of patients' mood, so the prevalence of DDs in the respective clinics should be more informative.

Head and neck cancer patients were more likely to be willing to be contacted if they had a self-rated PH of depression, but currently good levels of QoL. Therefore the HN sample had disproportionately high levels of patients with a PH of depression and fewer patients with a current DE, so it would be inadvisable to compare this sample to other cancer groups and previous studies. It is possible that the low level of DDs in this sample is genuine and possibly even unique to St Bartholomew's hospital but it is not possible to test that given this data.

4.7.2 Troubling symptoms

As expected CR cancer patients (and controls) reported higher levels of diarrhoea than the HN patients. Interestingly the CR cancer patients also reported higher levels of insomnia compared to the HN patients at first assessment. With regard to other QoL symptoms, the HN patients reported higher levels of symptoms on the HN module than previous reports[4, 176, 187]. Similarly the CR cancer patients also reported higher levels of symptoms then previous reports[28]. Despite the functional impairments, both sets of cancer patients reported reasonable global QoL levels, which did not differ between diagnoses and are only marginally lower then that of the general population (estimated mean based on a sample of 276 participants from a Norwegian sample was 72)[4]. This supports previous reports that global QoL levels compare to the general population in later cancer survivors, despite continued functional impairments.

4.7.3 Symptoms associated with depression

The most highly associated symptom associated with depressive symptoms in both sets of cancer patients was fatigue. The other variables closely associated with depressive symptoms were defaecation and body image problems in CR cancer patients and social contact problems in HN patients. Stoma problems were also associated with depressive symptoms in CR cancer patients, but could not be included in the multivariate analyses due to small numbers.

Fatigue is highly likely to be strongly associated with depressive symptoms, partly due to the high comorbidity of depression and fatigue. The other independently associated symptoms are symptoms unique to each cancer that are most likely to interfere with social functioning. Again, supporting previous literature that impaired social function is associated with increased depressive symptomatology[171]. As the ratings are self reported symptoms it is not possible to say whether the depressive symptoms are due to the social difficulties caused by the cancer diagnosis, or whether patients with higher levels of depressive symptoms are more distressed by social difficulties that may be related to their cancer.

In keeping with the HADS-D findings, the only independently associated symptom with an increased risk of a DE in CR patients was poorer body image, albeit less associated than a PH depression as rated by the clinical interview. As would be expected from a screening instrument, HADS-D was also associated with increased risk of a DD. Interestingly, PH depression as assessed by the interview, but not patient rated measures, was also associated with poorer body image, suggesting that PH clinical depression may lead to poorer body image, or that there is a third explanatory factor. Also, it should be noted that the confidence intervals for these findings are quite broad implying the results could be interpreted as having low reliability and a need for further studies with larger sample sizes is required.

4.7.4 Factors associated with poorer quality of life

The most highly associated symptoms with global QoL in CR cancer patients were depressive symptoms, problems with taste, dry mouth and sore skin. Stoma problems were also highly related, but due to small numbers were not included in the multivariate analyses. Taste problems and dry mouth are highly likely to be side effects of chemotherapy, providing more evidence towards persistent functional difficulties in cancer patients. However, as with HN cancer patients, past studies suggest that CR cancer patients treated with chemotherapy report similar global QoL scores as non chemotherapy patients[188]. Despite previous findings, sexual function was not independently associated with QoL, and there were no univariate associations between impotence or dyspareunia and poorer QoL. However, fewer patients completed the impotence and dyspareunia scales so this may be due to lower numbers or sample bias. Also, there was no difference between sexual function scores between CR cancer patients and controls as may be suggested by the literature. However, the CR control group was also evidently a symptomatic group, so perhaps also experience more problems with sexual function than healthy controls. The lack of patients with colostomies meant it was not possible to investigate the independent association of a stoma with mood or QoL and the univariate effects should be interpreted with caution. Although if the univariate effects are representative of the population, then for the effect to be significant in such a small sample implies it is of great concern to a select group of patients, so the issue of stoma complications should be investigated further.

Counter to the hypothesis, HADS-D was not independently associated with global QoL in HN patients. The only variables associated with poorer global QoL in HN patients were fatigue, pain, problems with social contact and increasing age. Fatigue and pain are symptoms that are often associated with depression, accordingly the univariate relationship between HADS-D and global QoL was confounded by fatigue. This indicates that whilst depressive symptoms were associated with global QoL, depressive symptoms were not independently

associated with poorer QoL, and fatigue had a stronger association with QoL than depressive symptoms. Unfortunately it is impossible to ascertain the origin of the fatigue, or the cause or effect relationship between depression and fatigue in a cross sectional analysis on cancer patients. HADS-D scores at T1 did not confound the model, but it is unlikely that depressive symptoms would lead to fatigue by a delay of over two years. In keeping with the hypotheses, problems with social contact was the only other symptom variable independently associated with poorer global QoL, supporting past work showing that interference with social function is important to overall QoL.

4.7.5 Limitations and conclusions

Despite a relatively good completion rate, the study is limited by the lack of completion by about 40% of patients. If there are differences in those that declined to complete the questionnaires or were missed by the researchers this may mean that the results are biased. Also, this highlights potential barriers of using questionnaires as a screening tool for depression. The 40% completion rate is despite the availability of a researcher for most of the study in the HN clinic and for half the study time period in the CR clinic. There are obvious barriers to completion, such as language difficulties and no reading glasses. Also many patients were reluctant to complete questionnaires about how they were feeling. However, the most pronounced barrier to higher completion rates was that many patients were missed by the researchers whilst the researcher was with another patient. This suggests that if questionnaires were to be used in clinics for screening purposes, the clinical team need to be involved in the distribution of the questionnaires.

The prevalence of DDs must be interpreted cautiously because those who met criteria to be contacted (e.g. indicated a PH depression) were more likely to provide their number, so in that sense the estimated prevalence based on those individuals who provided their contact number is probably over estimating the true

prevalence. It is because of this bias that the prevalence of PH depression was not calculated, as patients with a PH depression had not only been selected for by the study protocol, but also by self selection therefore likely to lead to a sizable difference between the estimated and true prevalence in the clinics. However, with regard to the prevalence of a current DE only those patients that were at risk of a DD on screening were interviewed, so false negatives would not be accounted for, leading to an estimated prevalence that is lower than the true prevalence in the clinics. This is likely to mean that some cases have been missed, but probably only a small number as the inclusion criteria for follow up was very broad and 60% of the CR patients and 50% of the HN patients were eligible for follow up.

There is also a possibility that the different operating procedures of the two clinics have affected the results. Firstly, different people were involved in the distribution and collection in the two clinics, so although the response rates are comparable, there may be differences in the population that were missed by the researchers. Also, HN patients are followed up at the clinic much more frequently then CR patients; unless there are any complications HN patients are issued follow up appointments every month after surgery for the first year, followed by a gradual decline in appointment frequency to once a year for 10 years. This is compared to a six to eight week post operative follow up for CR cancer patients, then a six month follow up and then the last follow up is at five years post treatment. Therefore, the time between diagnosis and completing the questionnaires may differ between the CR cancer and HN cancer group which may affect depressive symptoms and QoL. Also, since HN patients attend the clinic more frequently they may be more accommodated to the clinic setting, meaning the CR cancer patients might score higher on the HADS because of an increased emotional effect from being in the clinic. The results may also have been affected by differences in stage of cancer and type of treatment. This information was not available in this study, so it is not possible to test for differences or adjust for them. The analyses using the HN T2 data may also be slightly biased by the fact that those HN patients completed the questionnaire at home and not in a busy clinic setting, as was the

case previously and in the CR sample; this may have affected their mood at the time of completion. Also, the study does not include a general population control sample, so whilst it is possible to compare the results to that of previous reports on levels of depression and QoL measures in the general population, it is not possible to test for differences.

In conclusion, most of the findings from this sample support the previous literature; the levels of depressive symptoms are slightly higher than the levels you might expect in medical general practice samples, but still within the estimated range. However, the point prevalence of a DD appears to be within the range of the general population in the two clinics. Only 11 of the contacted CR non cancer patients were currently experiencing a DE which indicates an estimated prevalence of 14%. This is compared to an identical point prevalence in the CR cancer patients and 5% of HN patients. Whilst the point prevalence looks to be much lower in HN cancer patients, this is not significant. The apparent lower prevalence could be due to the sample bias towards those with a PH depression, but improved QoL and lower depressive symptom levels around the time of the interview. Suggesting that this sample has selected for patients with a PH depression but who are less likely to be suffering from a current episode.

Also, although the difference was not significant, it was surprising that HN cancer patients had lower levels of depressive symptoms then CR patients, given that the previous literature suggests that they would show higher levels of distress due to the greater functional impairment associated with HN cancer. As previously stated, this may be due to chance, but may also be due to the differences in clinic protocols.

Finally, the data show that both sets of patients have similar global QoL levels to that of the normal population. However, there are continued functional problems in both cancer groups (and the CR controls) as supported by past studies[146, 173]. This finding in some respect appears to contradict the finding of a relationship

between these functional difficulties and depressive symptoms and global QoL. The most likely explanation is that the effect sizes are small; the clinical implications of this are expanded on in the final discussion section of this thesis.

To summarise, the cross sectional study (part 2) of the thesis investigated the relationship between depression and QoL in a cross sectional sample. This part of the thesis partly addressed:

1. The first aim of the thesis; to measure the prevalence of DD in the CR cancer and HN cancer clinics at The Royal London and St Bartholomew's hospitals.
2. The first hypothesis that PH depression would be an important risk factor for a current DE in cancer patients.
3. The third aim of the thesis: to explore associations between other explanatory factors (such as symptoms) and depressive symptomatology.

The results showed no significant differences between any of the depression measures between the two cancer populations or between the CR cancer patients and CR controls. In keeping with the previous literature, cancer specific items that are likely to interfere with social function were the most likely to be associated with depressive symptoms. Similarly, depressive symptomatology (including pain and fatigue) were very strongly associated with poorer QoL, more so than any other cancer symptoms. The next section (part 3) of the thesis further addresses the aims of the thesis using a prospective design. Wherever possible the results are compared to these findings.

PART III

Prospective study

5 Prospective methods

The previous part described the methods and results to a cross sectional approach to investigating depression in cancer patients. This part explains the methods, background and results to a longitudinal study investigating potential markers for depression and poorer QoL in newly diagnosed HN or CR cancer patients. This chapter explains the recruitment, procedure and analysis for the study. The results from this study are presented in Chapters 6-10. Most of the methods are described in this section, with the exception of the multivariate procedure used in Chapter 10, which is reported along with the respective results.

Ethics approval was obtained (06/Q0605/144) from the East London and The City Research Ethics Committee three on 15 January 2007.

5.1 Participants

All newly diagnosed cancer patients who presented to the HN cancer clinic or CR clinic between March 2007 and March 2009 and who spoke English were eligible to take part in the study. See appendix 5. 1 for patient information sheet.

5.2 Evaluations

5.2.1 Demographic and cancer related variables

- Patient age on joining the study, sex, ethnicity and marital status were all recorded.
    - Marital status was recorded as: married, cohabiting, widowed, divorced/separated or single.
    - Self identified ethnicity was recorded for each patient, but due to low power, ethnicity was simply coded as white and non-white for analyses.
- Patients were asked their height and weight to calculate their BMI.
- Patients were also asked to provide information on smoking and alcohol consumption. If the patient could not be asked because they withdrew from the study or died soon after their treatment then the information was taken from their notes (where available).
- Information on comorbid disabilities (e.g. chronic obstructive pulmonary disorders (COPD), arthritis, ischaemic heart disease and diabetes) was recorded using patient reported symptoms and patient notes. Comorbid disabilities were coded from zero to two based on level of severity of symptoms, such that severe COPD would score two, whereas milder versions (e.g. controlled asthma) would score zero. Hypertension was scored as zero unless there was evidence of symptoms. Diabetes was

scored as one. The comorbidity rating was scored independently by a psychiatrist (AK) and one non-medic (JA) and then reaching consensus.

- Past or present alcohol abuse was assessed during the SCAN interview and through consensus with a psychiatrist.

- Tumour, node, metastases (TNM) staging was used as an indication of the extent of the tumour. T stage, N stage and metastases were all coded as separate variables.
- Treatment with adjuvant chemotherapy or radiotherapy was also recorded.
- A variable to code for surgical severity was also derived for the purposes of this study. The variable was scored from zero to five, with one point for each of the following criteria:
    - Colorectal cancer patients
        1. Length of operation
        2. Significant post operative complications
        3. Extended length of hospital stay
        4. Stoma formation
    - Head and neck cancer patients
        1. Length of operation
        2. Need for sophisticated construction
        3. Significant post operative complications
        4. Extended length of hospital stay
        5. Surgery resulting in adverse effect on aesthetics of function

The criteria were decided by consultation with surgeons and the surgeon made the rating for each of their patients.

5.2.2 Questionnaires and interview

The following were used:

- The HADS, as described in the evaluations section of chapter 3**.**

- The EORTCQ and the H&N35 module for HN cancer patients or the CR29 module for CR cancer patients as described in the evaluations section of chapter 3. The CR29 was only completed by the minority of CR patients because it was only available towards the end of the recruitment period.

- The Childhood Trauma Questionnaire- Short form (CTQ) (appendix 5. 1) – The CTQ is a 28 item inventory that provides a reliable and valid screening for history of abuse and neglect [189]. The CTQ has shown a consistent five factor structure assessing emotional, physical and sexual abuse and emotional and physical neglect with five items contributing to each subscale. A further three items assess a tendency towards minimising negative experiences known as the denial scale as a way of checking for social desirability effects. This scale asks questions such as: "There was nothing I wanted to change about my family". It is thought that few individuals would have always thought "There was nothing I wanted to change about my family" when growing up. Therefore answering "very often true" to such questions is thought to indicate possible minimisation of any negative memories. (Thus "very often true" is scored as one and any other answer is scored zero.) The greater the score on the denial scale, the greater the likelihood of minimisation. The CTQ correlates with clinician and therapist ratings of abuse and demonstrates excellent reliability in clinical and community samples[189]. Test retest reliability coefficients are reported to range from 0.79 to 0.86 over an average of four months. Internal consistency of the CTQ is excellent overall (alpha = 0.91) and acceptable for each subscale (0.58 for physical neglect, 0.69 for physical abuse, 0.83 for emotional abuse, 0.85 for emotional neglect and 0.94 for sexual abuse) in a community sample[190]. The scale can also be used as a total score through

combining all the subscales (not including denial). The total score was used in this study because total score was considered a more inclusive and sensitive measure.

• Eysenck Personality Questionnaire (EPQ) (appendix 5. 3) - The EPQ, first published in 1975, is a well validated questionnaire to assess personality traits[191]. The inventory consists of 88 questions and is considered to have a three factor structure assessing extraversion, NE and psychoticism and a 'lie' scale to indicate a bias towards socially desirable answers. Twenty-three questions relate to NE which is the scale of interest in this study. For each item, patients are instructed to answer 'yes' or 'no'; a yes answer scores one point and a higher score indicates a higher degree of NE. All four scales have been found to have high validity with alphas of 0.86, 0.83, 0.80 and 0.61 for extroversion, NE, lie and psychoticism respectively[192].

• The Brief Life Events Questionnaire (BLEQ) (appendix 5. 4) – The BLEQ screens for any significant LE in the preceding six months[193]. The questionnaire includes 12 events and participants are asked to indicate whether the event has happened to them in the last six months. If yes, then the participant indicates the level of distress caused by that event, choosing from 'very bad', 'moderately bad' and 'not too bad'. The questionnaire also has two open ended questions. The first asks whether anything has happened to them in their life that has caused them a lot of stress (and if so, what) and the second asks if they think anything has happened to them in their life that has caused them to feel depressed (and if so, what). Each item is scored to give an indication of the number of stressful LE that happened in the last six months, giving a total number out of 12. The questionnaire was also scored to include only responses that indicated a moderate or very bad level of distress. Finally, the questionnaire was also used as a scale where each item scores either zero (no event) one (not too bad) two (moderately bad) or three (very bad).

• The brief COPE (appendix 5. 5) - The brief COPE consists of 28 items relating to coping and support seeking strategies and is considered a reliable tool to assess 14 conceptually different coping styles[194]. Each item details a behaviour which may offer support (e.g. I've been taking action to try to make the situation better) and the participant is asked to indicate the level to which they usually use that type of support on a scale of zero to three. Each coping style scale is the sum of two items randomly placed in the questionnaire. The scales are shown below with respective Cronbach's reliability alpha:

- Active coping (0.68)
- Planning (0.73)
- Positive reframing (0.64)
- Acceptance (0.57)
- Humour (0.73)
- Religious coping (0.82)
- Use of emotional support (0.71)
- Use of instrumental support (0.64)
- Self distraction (0.71)
- Denial (0.54)
- Venting (0.50)
- Substance use (0.90)
- Behavioural disengagement (0.65)
- Self-blame (0.69)

Patients were asked to complete the questionnaire with respect to how they have coped with their cancer diagnosis.

- The SCAN interview as described in the evaluations section of chapter 2.

5.2.3 Physiological evaluations

5.2.3.1 Cortisol protocol

Saliva samples for cortisol analyses were collected in plastic salivettes, consisting of a sterile cotton swab inside a plastic tube (Sarstedt, UK). Patients were instructed to chew on the cotton swab for a minute and return the swab to the tube and store the salivettes in the fridge. Each kit contained nine labelled salivettes with patient identification and the appropriate measurement time (e.g. Day 1, PM), full instructions for sampling and a freepost envelope with which to return the samples. Patients were asked to take samples on waking, 30 minutes after waking and before going to bed on three consecutive days. Patients were also asked to write down the time and date of each sample, either on the tube or on the instructions checklist. Patients were asked not to smoke, eat or drink for 30 minutes before each sample. Patients were told that it was imperative for them to be honest about what time they took the sample and if they forgot a sample, to miss out that one and wait until the next sample was due. Full patient instructions are provided in appendix 5. 6.

Once patients had completed all nine samples they were instructed to post them in the first class envelope provided. On receiving the samples, the salivettes were centrifuged, and the saliva was aliquoted into eppendorf tubes and frozen at -20ºC until ready for analysis.

Samples were sent on dry ice to the Laboratories of Integrative Neuroscience and Endocrinology at the University of Bristol, under the care of David Jessop for radioimmunoassay. Intra and inter assay variability has been reported to be less than 5% and 10% respectively[195]. See appendix 5. 7 for full assay protocol.

5.2.3.2 Cytokine and CRP protocol

5ml blood samples were collected between 8am and midday, with the majority of samples collected between 8:30 and 10:00am. Blood was kept on ice before being centrifuged at 1500 rpm or 3000 rcf for 10 minutes at 4°C. Plasma was aliquoted into 5 x 200 µl aliquots and the remaining plasma aliquoted in 1ml volumes into appropriately labelled vials. The blood pellet was disposed of. The aliquoted plasma was snap frozen in liquid nitrogen and then stored at -80 until analysis.

Cytokine assays were conducted with a Meso Scale Discovery (MSD) multiplex imager (www.mesoscale.com) using the multi-spot human plasma protocol at the Centre for Cancer and Inflammation, Institute of Cancer, Barts and The London School for Medicine and Dentistry, Queen Mary University of London. The MSD small spot was found to be the most consistent and sensitive method for assessment of IL1ß and IL6 levels in human serum[196]. Average intra assay variation for IL6, IL1ß, TNFα and IFNγ was 4.52%, 5.40%, 3.33% and 2.82% respectively. In total nine assay plates were run. Average inter assay variation for the last five assay plates was 7.23%. Results taken from assays one to four were anchored to the fifth plate due to an unacceptable level of inter assay variation in previous assays, caused by using assay kits from different batches. Full cytokine analysis details can be found in appendix 5. 8.

C-reactive protein assays were carried out by the Glasgow Department of Clinical Biochemistry. Samples were sent on dry ice and were measured according to the Abbott Architect method. Intra and inter assay coefficients of variation (cv) are all reported to be <3% at 3 levels of quality control (see table 5.1).

Level	Mean CRP (mg/l)	Intra assay cv (%)	Inter assay cv (%)
1	5	1.02	2.15
2	18.1	0.32	0.49
3	73.3	0.50	0.54

Table 5.1: Coeffecients of variation for CRP assay results.

5.3 Procedure

All eligible patients were invited to join the study after confirmation of their diagnosis and treatment plan. All patients taking part gave written informed consent.

- See figure 5.1 for an overview of patient involvement.
- Before treatment, patients completed the HADS and EORTC-QLQ and the appropriate cancer specific module. Patients also took home the saliva sampling kit and were instructed to choose 3 days in which to take the saliva samples between the date of recruitment and their surgery.
- Blood samples were taken just before surgery (T1), one week after surgery (T2) and 6-8 weeks (T3) post surgery.
- The HADS and EORTC-QLQ were repeated at six to eight weeks (T3), three months (T4) and six months (T5) post operation.
- Patients completed the BLEQ at one (T3) and six months post treatment (T5).
- Patients completed the SCAN, COPE, EPQ and CTQ between three to six months after treatment.

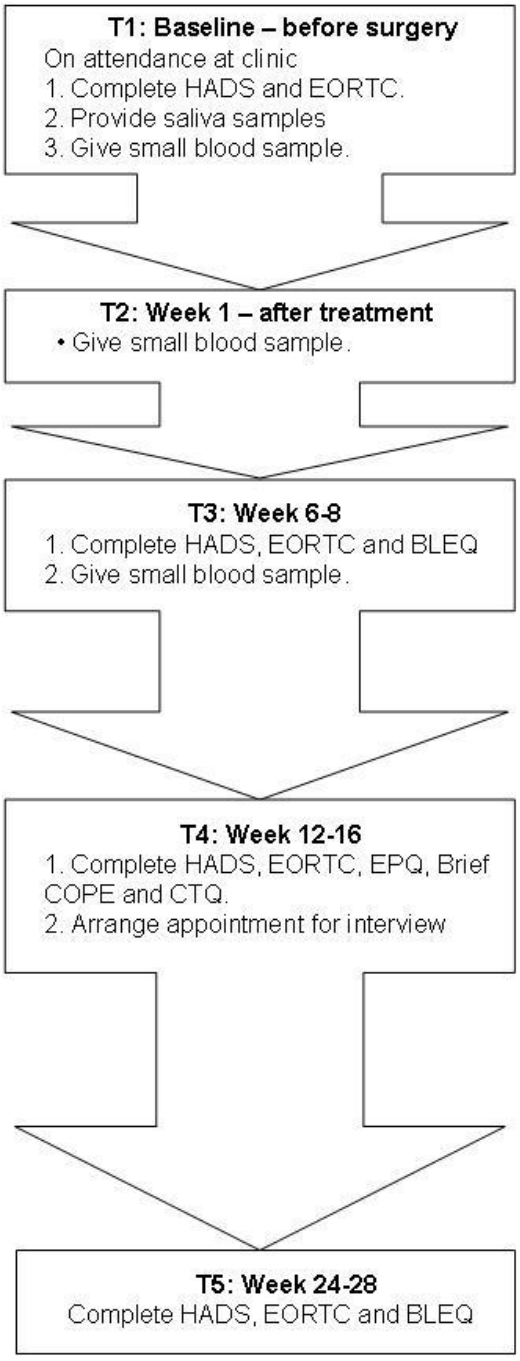


Figure 5.1: Flowchart depicting overview of questionnaire and sampling timetable.

5.4 Analyses

All ordinal variables (T stage, N stage, cormorbid disability) were treated as continuous. Treating ordinal items as categorical would reduce power and the relationships were expected to be linear

Past studies indicate that relatively small samples (50 patients) should be adequate to detect an association between the psychological variables and depressive symptoms[161]. The most power limited factor for this study was most likely to be the cortisol and cytokine analyses, due to the large variation between patients. The variation may be caused partly by measurable factors such as medication, smoking and body mass index (BMI) as well as harder to measure factors such as location of tumour in the case of saliva samples in oral cancers. Although some previous studies have found significant differences in IL6 in cancer patients with a DD compared to those without[139, 140], their analyses were non parametric, so no power calculation could be conducted. This study is considered as a predominantly exploratory pilot study to assess which variables give the greatest effect, thus informing future larger scale studies which can focus on the most promising variables.

5.4.1 Exclusions

For the most part an inclusive approach was taken to the data, as the questionnaires were self limiting and cancer patients are expected to have a wide range of cytokine levels, especially after surgery[197].

5.4.1.1 Questionnaire and demographic data

No individual patient questionnaire data was excluded from the study.

Due to power restrictions, items were excluded from multivariate analyses if fewer than 17 patients had completed the item. Seventeen was chosen as that was the lowest number of patients who completed all the main variables of investigation (CT, NE, LE or PH depression). Categories in categorical variables were excluded if less than seven patients were in that category. Ordinal data were also excluded if less than three patients scored higher than baseline in the variable.

As a result of the above exclusion criteria, questions regarding PH depression or DE were only investigated using both cancer groups, as too few patients had a DD for the analyses to be stratified. Due to low numbers:

- Ethnicity and metastases were excluded from further analyses.
- Radiotherapy was only used in HN analyses.
- Marital status was condensed into married and unmarried.
- Alcohol consumption was condensed into current drinker and teetotal.
- Smoking was condensed into never smoked, past smoker and current smoker.

The numbers for the new variables are given in the next chapter.

5.4.1.2 Recruitment and sample characteristics

Body mass index was also excluded from the multivariate analyses. Baseline BMI was taken, as it was a possible covariate of cytokine levels and depressive symptoms. Body mass index was not associated with any cytokine levels. Body mass index was not considered an appropriate covariate for depressive symptoms alone in CR or HN cancer patients, as BMI can change dramatically over the course of cancer development, diagnosis and treatment.

5.4.1.3 Physiological data

Despite the inclusive approach there were a few findings that appeared to be obvious outliers so these were removed from the dataset:

Most cortisol levels were between 0.2 and 5pg/ml. Any results which were over 15pg/ml more than the overall mean for that individual for that sampling time (when excluding the high finding) were excluded. This resulted in the loss of 10 samples, but no lost data points when analysing the means. One patient also had morning samples over 30 but did not sample on any other days so these data were excluded as the levels were over two standard deviations above the total group mean. This resulted in losing the morning samples of one patient.

All IL1ß data were excluded from analyses because the range was very small [mean(sd)=0.24 (0.40), median=0.08 range 0-3.52] and 66% of patients were below the level of minimum detection.

The IL6 data for one patient were excluded as the IL6 levels were over twice that of the second highest level and their IL6 levels did not correlate with their CRP levels [IL6 levels (pg/ml) T1=46, T2=391, T3=67]. All other cytokine and CRP results were retained.

Please see chapter 8 for summaries (including range) of included physiological measures.

5.4.2 Sample and data checks

1. Logistic regressions were carried out to check representativeness of the recruited sample with regard to demographic information.

2. Logistic regressions were carried out to check representativeness of sample at each study wave compared to patient wave non-completion or permanent patient loss.

3. Due to clinical restrictions there was some variation between date of diagnosis and treatment and completion of questionnaires and blood

samples. Linear regressions were conducted to test for an effect of time between

a. Diagnosis and cytokine levels, depressive symptoms and QoL.
b. Time between first and later blood samples.
c. Time between start of treatment and later cytokine levels, depressive symptoms and QoL.

5.4.3 Hypothesis testing

T tests or Mann-Whitney and Chi-squared analyses were used to test for differences between the two cancer groups. The results indicated some important differences between HN and CR patients, so for the purposes of the regression models, the analyses were stratified as the samples were too small to test for an interaction. Stratifying the results still allowed for (non statistical) comparison between the two groups and helped to prevent the possibility of misinterpreting effects that were only applicable to one patient group. However, it was not possible to stratify for analyses involving PH depression or DE6 due to low numbers, so for these analyses the groups were combined.

Linear regression models were carried out at each wave of data collection to check for associations between CT, NE, LE, PH depression and 1) depressive symptoms and 2) global QoL at each time point.

Logistic regression models were carried out to test for an association between CT, NE, LE, PH depression and development of a DE within six months (DE6) after treatment starts.

Multilevel regression analyses were used to investigate an overall effect of CT, NE, LE or PH depression on depressive symptoms or QoL using patient identity as the panel variable. This technique allows the relationships between variables to be investigated in all data waves through relaxing the assumption of independence

between the panel variable (see below). Multilevel regression was also used to test for an interaction with time, to indicate whether the strength of any relationship is greater at later time points.

Multiple tests were required to test the many hypotheses. No correction for multiple testing was made, due to the small sample size and pilot nature of the study that could increase the risk of false negative findings. Thus, anomalous findings were interpreted with caution and the p values were presented in order to give an indication of the strength of the association and therefore whether the association is worthy of further investigation.

5.4.3.1 Regression assumptions

As stated in Chapter 2, robust standard errors were used in the analyses. Unfortunately, due to computational restrictions it was not possible to use robust standard errors in multilevel logistic regression.

The associations found using robust errors were also checked using bootstrapped standard errors. Bootstrapping works by taking numerous sub samples of the data and then averaging out the standard error terms, thus the confidence intervals (CIs) are less likely to be skewed by extreme values. Bootstrapping is considered to be useful in smaller samples and in non parametric samples. However, bootstrapping has been criticised for reporting 95% CIs which aren't truly representative of 95% of the population, resulting in a bias towards positive results[198]. To prevent a bias towards positive results the analyses were also run using 99.99% CIs, which showed the same results as using 95% CIs. Nevertheless, in order to be extra conservative, bootstrapping was only used to check any significant results from using the robust standard errors. Using bootstrapped standard errors made no difference to the psychological results, but it did make a difference to the physiological results. Due to the inclusive approach with the physiological data it was possible that the results were skewed by outliers,

thus regressions for the cytokine and cortisol analyses were rerun using bootstrapped standard errors and both results are reported. The final multivariate models were also checked using bootstrapped standard errors. Unfortunately, due to computational restrictions it was not possible to use bootstrapped standard errors in multilevel logistic regression.

5.4.4 Missing data

5.4.4.1 Missing single items

Missing items on the HADS and EORTC-QLQ were dealt with as described in the main methods in Chapter 2. Seven patients were missing an item on one or more scale, thus their scores were inferred by using the mean of the remaining six items. No patient had more than one item missing on either scale for the HADS. Fifteen patients were missing single items on the multi-item scales in the core EORTC-QLQ (not including the functional scales). Similarly another 37 on the H&N35 and 15 on the CR29 were imputed. Many more single items on the EORTC-QLQ were missing and were treated as missing data.

Missing items on the CTQ were imputed using a mean of the other four items on the subscale, provided that only one item was missing on the subscale. If the patient missed out an item on the denial scale, the denial score was simply the total of the other two items. Six patients had imputed data on one or two scales and four patients had a missing item on the denial scale. No patients missed more than one item on any one scale or were missing more than two items overall. There was no apparent pattern to which items were missed.

Missing items on the EPQ-N scale were assumed as ‘No’ answers therefore potentially biasing towards lower NE scores in these patients. Five patients were missing one item, two patients missed two items, one person missed three items, two patients missed five items and two patients missed six items (out of 29 possible items).

Items on the BLEQ were treated as if no LE had occurred, potentially biasing towards lower levels of LE. Seven people missed one item (three at T3 and four at T5), four people missed two items (one at T3 and three at T5) and one person missed three items (T3). Two patients missed seven items so their LE data were discarded.

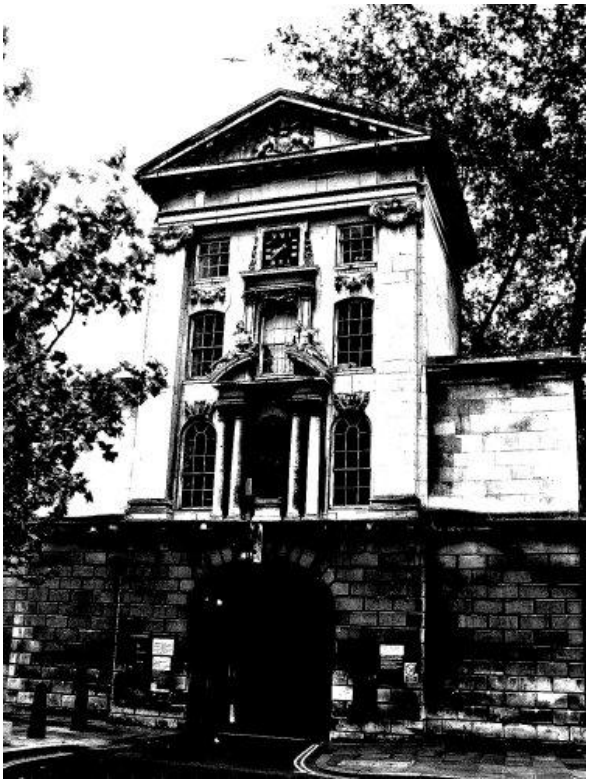
Only three people missed one item on the COPE. There are no specific instructions for dealing with missing items on the COPE. As each scale consists of two items, in cases of one missing item, the score of the completed item was doubled to be representative of a two item scale score. One person missed thirteen items on the COPE and their COPE data were discarded.

5.4.4.2 Missing scales or measures

There were relatively few missing data for each of the measures, apart from on the H&N35 and CR29 modules, due to the late introduction of those modules to the protocol. Complete case analyses were conducted. In the case of the multivariate analyses further post hoc tests were carried out to check the patients in the final model were representative of the univariate analyses (please see multivariate methods in chapter 10). Missing data numbers are reported in the next chapter.

5.5 Summary

This chapter explained the data collection and the procedure for the analyses for the following results chapters. More detail on the multivariate analyses is given in chapter 10.



6 Recruitment and sample characteristics

This chapter focuses on the following:

1. Measurement of the prevalence of DDs in the two cancer clinics (aim 1 of the thesis –section 1.6.1)
2. Testing the hypothesis that depressive symptoms are strongly related to poorer QoL in cancer patients (hypothesis 1, section 1.6.1)
3. Introducing the dataset that is used in the following results chapters.
4. Describing the recruitment, patient characteristics and representativeness for the prospective study. The demographic and cancer related variables are presented, as well as the prevalences and means of depressive symptoms, global QoL scores and incidence of a DE6.

The background to this section briefly covers the expected prevalences of both depression measures and the levels of QoL in this population as well as the rationale behind the hypotheses. The discussion summarises the results and compares the results to that of the cross sectional data in chapter 4.

6.1 Background

It has been suggested that HN cancer patients experience higher levels of depressive symptoms[185] compared to patients with other types of cancer, but a closer inspection of the literature suggests that this may not be the case and depressive symptom levels are not especially high in ambulatory HN patients compared to other cancer patients[121, 186]. However, a transient rise in depressive symptoms following diagnosis has been described in HN patients which is more marked than in those with CR cancers[146, 169]. This could be explained by the immediate high impact of HN surgery on patients' function and appearance and the increased used of radiotherapy in treating HN patients compared to CR patients. However, very few prospective studies have focused on mood and QoL in CR patients and the majority of QoL studies have studied patients over one year past diagnosis.

Based on the research reported above, the prevalence of a DD would be expected to be similar to that found in the general population (only slightly higher then that of a 6 month prevalence)[125], which has been reported to be between 10 and 20%[59, 60, 199]. No major differences were expected between the two samples in terms of depression or QoL. HADS-D scores were expected to be highly correlated with global QoL at each data wave as reported in the cross sectional study (chapter 4).

6.2 Patient recruitment

Figure 6.1 details the flow of patient recruitment and attrition. Overall 58% of eligible HN and 71% of eligible CR patients (total 65%) took part. The reason for lower participation of HN patients was most likely because HN patients were often "fast tracked" with surgery taking place within a few days of diagnosis and therefore there was less opportunity for patients to be contacted before treatment. Forty-one HN and 22 CR patients completed the study. There was a total of 20 HN and 18 CR patients who either withdrew from the study (five HN and six CR), died

(seven HN, seven CR) or were lost to follow up for other reasons (details shown in figure 6.1).

There was no difference between demographic variables in patients who took part compared to those who were uncontactable before their treatment or who refused to take part. Although, there was a trend for younger patients taking part *[N=163, p=0.071*]. Full details are shown in appendix 6. 1.

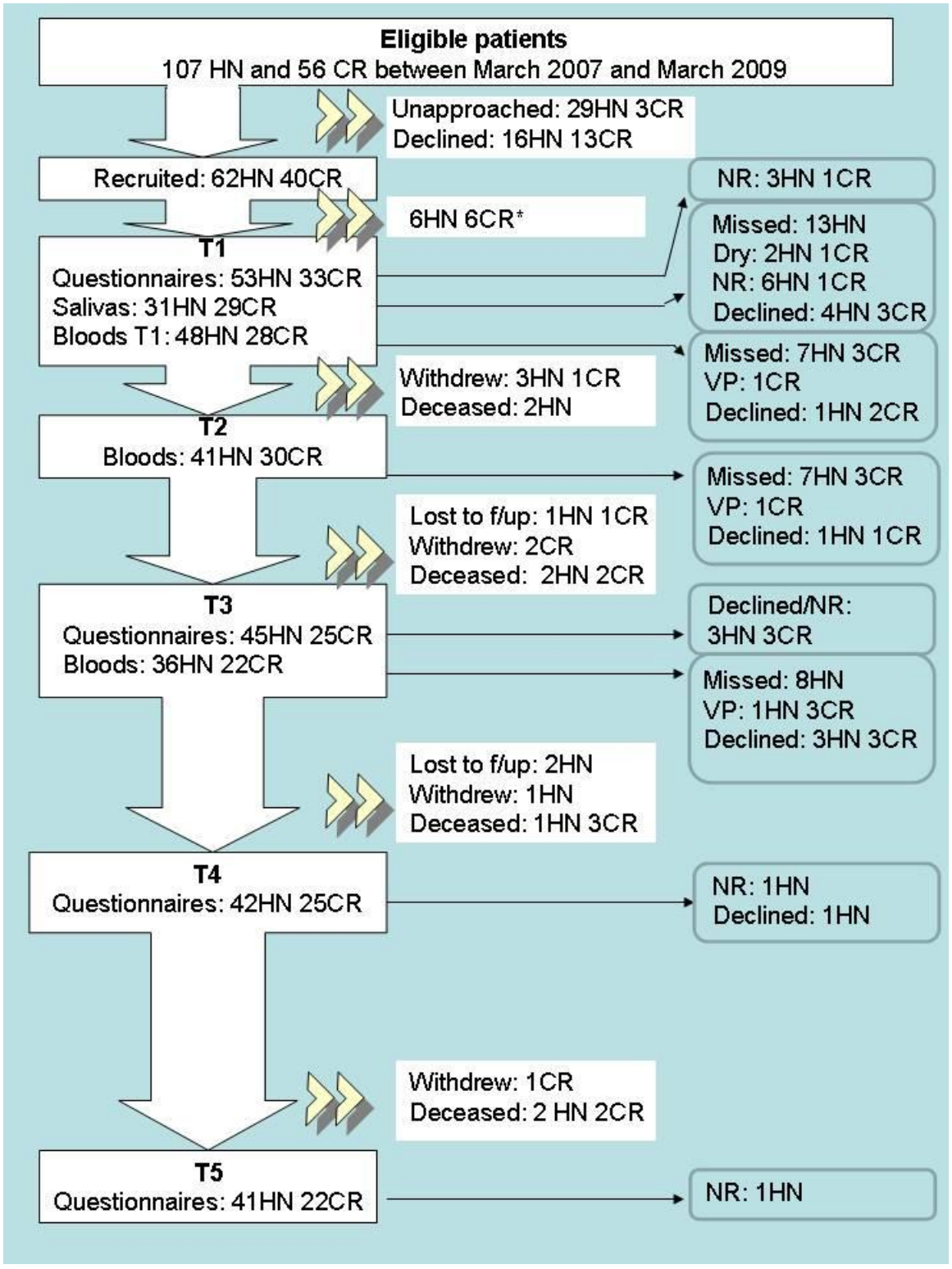


Figure 6.1: Consort diagram for prospective study. Permanent patient loss and reasons is shown in the centre. Temporary loss of patient data and reasons is given on the right. NR=Not returned or received, VP=Venepuncture problem *HN 1 benign, 2 too extensive disease, 1 went private, 1 excluded due to cognitive impairment, 1 dropped out. CR: 1 benign, 1 went private, 2 changed treatment, 2 dropped out.

6.3 Questionnaire reliability

With the exception of a few scales on the EORTC-QLQ CR29 where very few patients completed the scale, or where there was little variation between scores, all the questionnaires used in the study show acceptable reliability (Cronbach's alpha>0.60) with the majority showing good internal consistency. See appendix 6. 2 for Cronbach's alphas for each questionnaire scale.

6.4 Representativeness

Logistic regression analyses were conducted for each wave of data collection to investigate differences between those who took part compared to those who did not, as detailed in section 6.2 (including permanent and temporary exclusions).
Type of cancer did not affect whether patients completed each wave of data collection. The data were representative at each wave with the following exceptions:

- Patients with higher IL6 levels at baseline were less likely to provide the T2 blood sample.
- Those who took part in T2 and T3 waves (but not T4 or T5) of data collection were younger then those that did not.
- From T3 onwards patients who took part had fewer comorbid illnesses and lower cytokine levels at T2.
- Patients who took part in waves T4 and T5 also had lower IL6 and CRP levels at T3, but higher levels of IFNγ.
- All other variables were non significant.

All of the significant results for T2, T3, T4 and T5 are presented in appendix 6. 3 to appendix 6. 6 respectively. Appendix 6. 7 presents an example of the all of the variables tested using T5.

These findings are consistent with the fact that some patients with very high levels of inflammation died soon after their operation and those with greater disability were more likely to struggle with taking part in the study alongside the cancer and their other illnesses.

6.5 Effect of time

There was a significant effect of time taken from diagnosis to first blood sample on TNFα at T1 in CR patients *[N=28 ß(CI)=0.02 (0.00 to 0.05) p=0.039]*. If a model was found to be significant the model was adjusted for the time taken from diagnosis to first blood sample and it did not affect the model.

IFNγ levels were significantly associated with time between the blood sample at T1 and T2 *[N=39 ß(CI)=0.10 (0.00 to 0.19) p=0.041]* in HN patients, but this did not affect any of the findings when models were adjusted for the amount of time between samples. Also the time from starting treatment to T3 global QoL measurements and T4 HADS-D measurements were associated. With longer time associated with poorer QoL at T3 and increased HADS-D at T4 *[N=45 ß(CI)=-0.34 (-0.67 to 0.00) p=0.047; N=42 ß(CI)=0.04 (0.01 to 0.07) p=0.022; respectively]*.

6.6 Patient characteristics

Table 6.2 shows the baseline demographic characteristics of the sample. To summarise, the mean (standard deviation [sd]) age of patients at baseline was 66 years (12.47), although CR patients were significantly older and had significantly more comorbidities.

Measure		CR	HN
N		35	56
Age*	**mean (sd)**	**70.41 (9.91)**	**62.61 (13.03)**
Sex			
	Male	17 (48.57)	32 (57.14)
	Female	18 (51.43)	24 (42.86)
BMI		27	41
N		25.87 (4.29)	25.29 (4.53)
Mean (sd)			
Ethnicity			
	White	31 (88.57)	48 (85.71)
	Other	4 (11.43)	8 (14.29)
Married			
	No	13 (39.39)	15 (27.78)
	Yes	20 (60.61)	39 (72.22)
Comorbidity rating*			
	0	**11 (33.33)**	**30 (60.00)**
	1	**10 (30.30)**	**12 (24.00)**
	2	**12 (36.36)**	**8 (16.00)**
Missing		**1**	**6**

Table 6.1: Demographics for all patients at baseline. N(%) unless otherwise stated. *$p<0.05$.

Table 6.2 shows the prevalence of smoking and alcohol consumption in the two patient groups. HN patients were more likely to smoke and have a history of alcohol abuse. However, the difference in smoking was only statistically significant if smoking was categorised into five groups, the effect was reduced to a trend when smoking habits were categorised into the three groups that were used in multivariate analyses.

Measure		CR	HN	significance
Smoking				
	Never	10 (40.00)	12 (25.00)	
	Past	12 (48.00)	19 (39.58)	
	Present	17 (12.00)	17 (35.42)	$\chi^2(2)=4.79, p=0.09$
Alcohol				
	No	8 (36.36)	8 (17.78)	
	Yes	14 (63.64)	37 (82.22)	$\chi^2(2)=2.81, p=0.10$
Alcohol abuse				
	No	**33 (100)**	**39 (82.98)**	
	Yes	**0**	**8 (17.02)**	$\boldsymbol{\chi^2(2)=6.24, p=0.01}$

Table 6.2: Smoking and alcohol consumption in all patients at baseline. Reported as N(%).

Table 6.3 shows the cancer-related information for HN and CR patients. Colorectal patients tended to have more extensive tumours than HN patients; most CR patients had T stage III, whereas most HN patients had T stage I tumours. Colorectal patients were also more likely to have metastases, whereas HN patients were more likely to be treated with RT.

Measure		CR	HN	significance
T stage				
	I	**2 (5.88)**	**23 (41.82)**	
	II	**6 (17.65)**	**12 (21.82)**	
	III	**20 (58.82)**	**8 (14.55)**	
	IV	**6 (17.65)**	**12 (21.82)**	
Missing		**0**	**1**	***$\chi^2(3)=23.11$, $p<0.001$***
N stage				
	0	21 (63.64)	33 (63.46)	
	I	7 (21.21)	6 (11.54)	
	II	5 (15.15)	13 (25.00)	
Missing		1	4	*$\chi^2(2)=2.16$, $p=0.34$*
Presence of metastases		**6 (17.65)**	**1 (1.79)**	***$\chi^2(1)=7.42$, $p=0.01$***
Surgery		33 (97.06)	54 (96.43)	*$\chi^2(1)=0.03$, $p=0.87$*
Chemotherapy		13 (44.83)	15 (29.41)	
Missing		5	5	*$\chi^2(1)=1.93$, $p=0.17$*
Radiotherapy		**1 (3.45)**	**24 (47.06)**	
Missing		**5**	**5**	***$\chi^2(1)=16.37$, $p<0.001$***
Recurrence		1 (2.94)	8 (14.29)	*$\chi^2(1)=3.03$, $p=0.08$*
Deceased		7 (20.59)	10 (117.86)	*$\chi^2(1)=0.10$, $p=0.75$*
Cause of death				
Cancer		3 (50.00)	5 (55.56)	
Cancer recurrence		1 (16.67)	4 (44.44)	
Other		2 (33.33)	0	
Missing		1	1	*$\chi^2(2)=3.85$, $p=0.15$*

Table 6.3: Descriptives for cancer related variables for all patients at baseline. Reported as N (%).

6.7 Depression and quality of life

6.7.1 Prevalences and means

Figure 6.2 shows HADS scores indicating the proportion of possible or probable (score of >7) cases for a depressive or anxiety disorder for each diagnosis and at each data wave. There were no differences between the cancer groups, with

relatively few patients showing signs of possible or probable depression at T1. There was a general trend towards increasing number of cases towards T4, which then declined back to levels similar to baseline by T5. The figures are provided in appendix 6. 8.

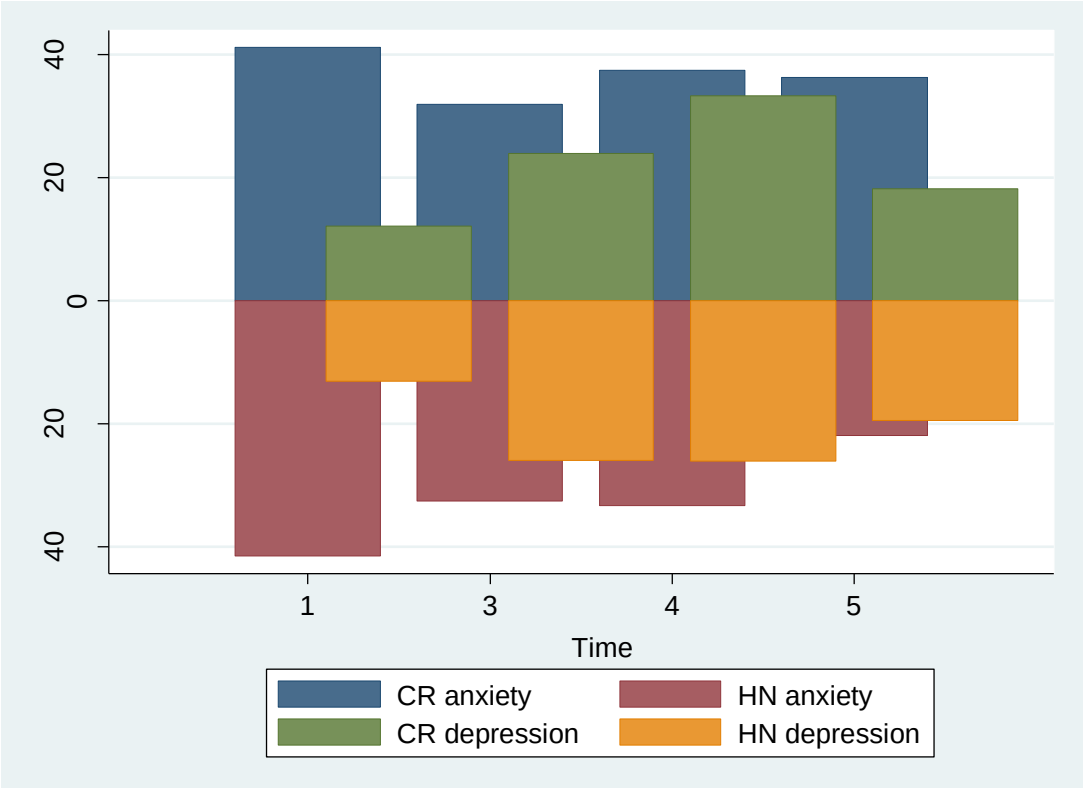


Figure 6.2: Prevalence of case level anxiety and depressive symptoms by time for CR and HN cancer patients based on a score >7 on the respective HADS subscale

Figure 6.3 presents the mean values of HADS-D scores for CR and HN patients over time. Longitudinal analyses showed that there was a significant effect of time in the HN group showing increased HADS-D scores at T3 and T4 compared to T1 and no significant difference between depressive symptoms at T5 and baseline. There was a similar but non-significant trend in the CR group, and the effect was even more pronounced when both groups were combined. These effects were still significant after adjusting for global QoL scores (appendix 6. 9). The means, medians and standard deviations of the HADS and global QoL scores are provided

in appendix 6. 10 and appendix 6. 11 respectively. The regression coefficients for the effects of time are provided in appendix 6. 12 and appendix 6. 13, respectively.

Figure 6.3 also shows the mean global QoL scores for CR and HN patients over time. There was a significant difference in QoL scores in HN patients at T3 compared to baseline, but there were no other significant differences. Also, the significant difference between T3 and T1 in QoL scores was no longer significant after adjusting for HADS-D scores (appendix 6. 14).

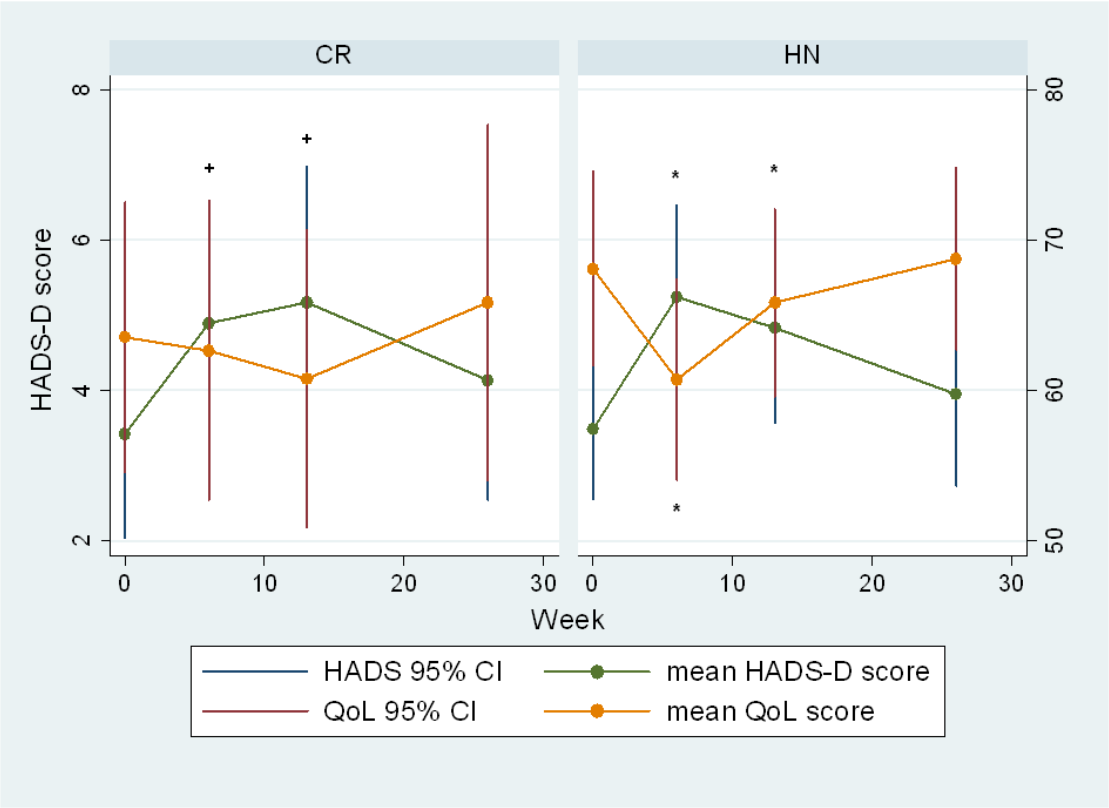


Figure 6.3: Mean HADS-D and global QoL scores over time for each diagnosis. + *p<0.10*, * *p<0.05*. Symbols signify significance of difference compared to baseline. Upper symbols for HADS-D, lower symbols for QoL.

Table 6.4 shows prevalences of an anxiety disorder or DD. The prevalence of a DE6 was 12.50% for CR cancer patients and 21.43% for HN cancer patients. Again, there were no significant differences between the two groups.

	CR N(%)		HN N(%)	
PH depression				
N	26		39	
Y	3	**(10.34)**	8	**(17.02)**
DE within 6 months				
N	21		33	
Y	3	**(12.50)**	9	**(21.43)**
PH of anxiety				
N	26		43	
Y	3	**(10.34)**	3	**(6.52)**
Anxiety within 6 months				
N	21		39	
Y	3	**(12.50)**	3	**(7.14)**

Table 6.4: PH of depressive or anxiety disorder and 6 month incidence of depressive or anxiety episode

6.7.2 Association between HADS-D and global QoL

Depressive symptoms and global QoL were strongly correlated in both sets of patients at each time point (table 6.5 and table 6.6).

N	Time point	ß (CI)	P value
32	*T1*	*-4.99 (-6.18 to -3.80)*	*<0.0005*
25	*T3*	*-4.24 (-6.58 to -1.92)*	*0.001*
24	*T4*	*-2.03 (-3.88 to -0.18)*	*0.033*
21	*T5*	*-4.91 (-6.93 to -2.89)*	*<0.0005*

Table 6.5: Coefficients and p values for associations between HADS-D and global QoL at each time point in CR patients

N	Time point	ß (CI)	P value
52	*T1*	*-4.08 (-5.48 to -2.68)*	*<0.0005*
45	*T3*	*-4.40 (-5.31 to -3.50)*	*<0.0005*
41	*T4*	*-2.74 (-4.15 to -4.53)*	*<0.0005*
40	*T5*	*-2.48 (-3.93 to -1.03)*	*0.001*

Table 6.6: Coefficients and p values for associations between HADS-D and global QoL at each time point in HN patients

HADS-D and global QoL were also highly associated when viewed over 6 months in both CR and HN patients *[CR:N=102(34), ß(CI)=-3.74 (-4.93 to -2.56) p<0.0005; HN:N=178(56), ß(CI)=-3.12 (-3.87 to -2.38) p<0.0005]*. Including an interaction with time indicated a significant interaction between T4 and HADS-D on QoL *[p=0.009]*. This appeared to be mainly due to the interaction in the CR patients, hence the lower association between HADS-D and global QoL at T4 in CR patients (compared to other time points).

6.8 Discussion

6.8.1 Recruitment

The results indicate that a high proportion of patients agreed to take part in the study and very few measures were excluded from the dataset. Unfortunately, as may be expected, those patients who continued to take part tended to be healthier. For questionnaire data completed at T3 and T4 a delay in completion was associated with higher depressive symptoms and poorer QoL. This was most likely because these patients were unable to complete the questionnaires on time due to complications and distress. Thus higher levels of symptoms were associated with poorer compliance to the protocol.

There were some marked differences in demographic and cancer related variables between the two cancer groups (particularly, smoking, levels of CT and inflammation), therefore the groups were analysed separately for the remainder of the analyses whenever the samples were large enough. However the number of patients with a PH of depression or current DE was too low for stratified analyses, thus these analyses were not stratified by diagnosis. Summaries for the investigated variables are presented at the beginning of the chapters on psychological and physiological factors respectively and relevant differences are highlighted.

6.8.2 Depressive symptoms and quality of life

The mean HADS scores and proportion of patients with high HADS levels was not significantly different between the two groups. As expected, there was an increase in HADS-D levels after diagnosis, which then fell back to baseline levels. Interestingly, this pattern was present in both the CR and HN cancer patients, despite the previous literature suggesting that CR cancer patients would be more likely to start with high levels of depressive symptoms which gradually decline over time[169]. However, the increase in depressive symptoms at one month and three months post surgery was only significant in the HN sample, suggesting a smaller effect in the CR group, although lower power cannot be ruled out as an explanation. The mean HADS-D scores at six months post surgery (4.14 and 3.95 for CR cancer and HN cancer respectively) were similar to the mean HADS-D scores found in the cross sectional study (4.80 and 4.91 for CR and HN respectively).

With respect to QoL scores, again there was no significant difference between the two diagnoses. However, in this case there was very little difference in the QoL scores in the CR cancer patients over time, whereas the HN cancer patients showed a significant drop in QoL one month post surgery. This may be related to the extent of surgery or radiotherapy: at this point some of the HN patients would still be learning to speak and eat again and/or starting adjuvant radiotherapy.

Consistent with the findings from the cross sectional study, HADS-D and global QoL were highly associated. As stated previously, levels of depressive symptoms were significantly higher at one and three months after surgery. Interestingly, in the longitudinal analyses the QoL of CR cancer patients did not vary significantly over time. There was a significant decrease in QoL scores in HN patients at one month post surgery. However, there was no significant difference over time in QoL scores in HN patients after adjusting for depressive symptoms. Whereas, the change in depressive symptoms over time was significant even after adjusting for

global QoL scores. This suggests that what little change there is in global QoL scores is related to depressive symptoms, whereas depressive symptoms vary independently of QoL. However, this may be because the HADS is a more sensitive measure then the global QoL score.

6.8.3 Depressive disorder

The percentage of CR patients with a PH depression was comparable to that of the general population (10%). More HN cancer patients had a PH depression (17%) than would be expected given the level in the general population. Though the difference between CR and HN patients was not significant, the trend is consistent with the theory that HN patients are more likely to have a PH depression as many of the behavioural risk factors for HN cancer (e.g. tobacco and alcohol use) are associated with a DD.

The incidence of a DE6 was similar to the proportion of patients with a PH depression; 13% for CR cancer patients and 21% for HN cancer patients. Although, if rates of depression are higher in less healthy individuals, these rates are probably substantially affected by the trend towards healthier individuals remaining in the study. Again, the rates are not significantly different between the diagnoses. The rate in the CR patients was similar to the point prevalence found in that of the cross sectional study (14%). However, the rate in the HN patients was much higher than that in the cross sectional study (5%) (chapter 4) and that is reported in previous literature[121]. This suggests that either biases in the cross sectional HN study led to a lower than true estimation of the point prevalence in that particular clinical sample or that only recently diagnosed HN patients are at increased risk of a DE. The incidence of a DE6 in CR patients was similar to that of the general population and supports the more recent opinion that rates of DDs in (curative) cancer patients are similar to that of those in general medical primary care patients[125]. On the other hand, the incidence of a DE6 in HN patients was quite high at 21%. Although this may not be significantly different from that of the

general population, it does indicate that more studies with larger samples are needed to investigate the prevalence of a PH depression and DEs in HN cancer patients using a structured diagnostic interview. This would help answer the question whether HN cancer patients are at increased risk of a post operative DE and whether this can be attributed to a greater likelihood of their having a PH depression.

6.8.4 Conclusions

In summary, this chapter introduced the data set for the following results chapters and reported and compared the levels of depressive symptomatology and QoL in the two cancer patient samples. Healthier individuals tend to remain longer in the study compared to those with greater disability which may be expected in a prospective study on newly diagnosed cancer patients. This chapter addressed the first aim of the thesis and reported the prevalence of depression in the CR and HN cancer clinics. The levels of depressive symptoms are similar in the two cancer groups, though there was a non-significantly higher incidence of a DE6 in the HN group. The study also tested the hypothesis that depressive symptoms will be strongly related to poorer QoL. As with the cross sectional data, HADS-D and global QoL were highly correlated, but the extent of this relationship varied over the study period and HADS-D scores appeared more susceptible to change then the global QoL scores. The following chapters report the relationship between the investigated psychological and physiological markers and depression and QoL scores.

7 Role of psychological factors

The previous chapter described the sample and the relationship between depressive symptoms and QoL. This chapter aims to:

1. Test the first hypothesis of this thesis: that patients with a PH depression are more likely to experience a DE following a cancer diagnosis.
2. Explore the associations between other explanatory factors of depressive symptomatology and QoL.

The chapter will address these aims by reporting on the relationship between the psychological variables included in the study (CT, NE, LE, PH depression and coping) and the risk of increased depressive symptoms, DE6 and/or poorer QoL.

Firstly the literature on psychological variables and methodological issues is reviewed, followed by a summary of the data, the main findings and a brief discussion.

7.1 Background

Depression has a complicated aetiology and the currently accepted view is that a combination of early life and ongoing stress increase the risk of a DD in those who are vulnerable through genetic predisposition (reviewed in section 1.2) Kendler and colleagues[62] (2002) proposed a very comprehensive model of the development of a depression and risk for a DE in women. This model included genetic risk, CT, NE, low self-esteem, early and mid life psychiatric problems (including anxiety, conduct disorder and drug misuse), low education, stressful LE, PH of depression and low social support as risk factors for a DE in the past year. This study has since been replicated and extended to include male participants by Sjöholm's group[200] (2009). There are still other variables that may contribute to the risk of a DE, such as low socio-economic status, low self-esteem and coping strategies[201]. Including all the psychological variables involved in the aetiology of depression is beyond the scope of this study. As the study also investigates physiological mechanisms that are particularly related to stress, the psychological variables related to stress are included.

Studies investigating the risk of a DE following a cancer diagnosis have often focused on the impact of cancer related variables, and there is less focus on non cancer related risk (see background in section 3.1.3). Of the studies that have investigated pre-cancer factors, most have been of breast cancer patients and there has been very little focus on HN patients and even less on CR patients. This study focuses on the relationship between CT, NE, LE, PH depression, coping and depression.

7.1.1 Childhood trauma

Childhood trauma can include many types of adversity occurring during childhood, such as family problems, neglect, abuse or experience of natural disasters. There is good evidence for CT as a risk factor for DD in the general population[202].

Retrospective reports on childhood adversities have shown that early stress is associated with occurrence of first DE and increased persistence of DD; although only abuse and not neglect was associated with persistence[203]. Similar findings have been reported in case control studies by other groups using a retrospective childhood abuse questionnaire (the Childhood Trauma Questionnaire [CTQ]). However, some groups found no such association with persistence[75]. One prospective case control study reported a relationship between past CT and risk of MDD in a sample of 1196 participants where the abuse was severe enough to involve a court hearing[73]. Childhood trauma reports have also been found to be associated with depressive symptoms[204]. Thus, in the present study CT would be expected to show an association with increased levels of depressive symptoms and increased risk of a DE6 in both groups of cancer patients.

Results from CT studies should be interpreted with due caution as mood congruent memory biases may increase reports of CT in those who feel depressed at the time of completing questionnaires[205], thus ideally data would be collected prospectively, but that was not feasible in this study. Also, despite reservations regarding the efficacy of CT questionnaires, one review found that, counter to most expectations, retrospective reports of CT tend to generate more false negatives than false positives, though the bias is not sufficiently great to invalidate results[206]. Furthermore, although there may be different relationships between specific categories of CT (such as sexual or physical abuse) with depression, there is also evidence of strong associations between different types of abuse[207]. Thus, in this study the total score of the CTQ was used.

7.1.2 Neuroticism

Neuroticism is a personality trait which is characterised by a tendency towards anxiety driven cognitions and negative affect. Neuroticism is known to be a risk factor for a DD in non cancer patients[208] and is significantly associated with genetic risk for a DD[62] as was introduced in section 1.2.2. Neuroticism is also

strongly related to levels of depressive symptoms[209]. The association between NE and depressive symptoms has been replicated in breast cancer patient samples, both three and six months after treatment[210, 211]. Similar results were reported in a group of 200 HN cancer patients[212]. The association between NE and depressive symptoms extended to poorer QoL and increased cancer related symptoms[212]. Therefore, NE appears to be a likely risk factor for increased depressive symptoms and DE in HN and CR cancer patients.

7.1.3 Stressful life events

Stressful LE in adult life, as opposed to childhood adversity, such as divorce, financial crisis or an illness, are known to increase the risk of a DE in the general population[213]. A few studies have investigated the effects of non cancer related stressors and depressive symptoms in cancer patients. Severe non cancer related difficulties were associated with a DE from four months to five years after diagnosis in a sample of 222 breast cancer patients[214]. Thus, non-cancer related LE are likely to increase the risk of a DE. Although interviews are considered to be the best method to assess LE, these are time consuming and would add a further burden on participants in an already intense study. Questionnaires, whilst slightly less reliable, are still widely considered to be valuable measures to capture the experience of major events[75]. This study uses the Brief Life Events Questionnaire (BLEQ) to assess total LE around the time of the cancer diagnosis. The BLEQ includes a list of 12 possible LE from a larger checklist of 67[3] and is considered to be a reliable measure of external life stressors[193, 215].

7.1.4 PH depression

One of the strongest predictors of a DE is a PH of depression[62]. The average age of onset of a DD is 25 years[199] whereas CR or HN cancers are more likely to

[3] The original list was devised from a survey using free text to report major LE and 82.5% of the reported LE are covered by the 67 item inventory. The chosen 12 accounted for 77% of the LE on the 67 item inventory.

occur in patients over the age of 50. Therefore, most cancer patients with a genetic vulnerability to a DD are likely to have already experienced a DE. Burgess and colleagues[214] found that past psychological treatment was a risk factor for a DE from one month to five years after a diagnosis of breast cancer, using the same sample as the LE investigations. Thus, PH depression is also likely to be a risk factor for increased depressive symptoms and development of a DE in CR and HN cancer patients. The most reliable way to assess a PH of depression is by using a diagnostic clinical interview such as the SCAN.

7.1.5 Coping

There is substantial literature on the effects of coping on depression and QoL in cancer patients. Coping refers to the efforts made to tolerate negative consequences of internal or external demands[216]. The study of ways of coping is a complex area involving aspects such as personality, threat appraisal and present environment. Past studies on coping have devised broad (not necessarily mutually exclusive) categories, such as emotional focused vs. problem focused and active coping vs. avoidance. Coping can also be defined by form of support such as religious coping, instrumental social support (practical support) and emotional support or voluntary and involuntary forms of coping. Also, different methods of coping may be adaptive in some circumstances, but less so in others. For example, a study investigating pre surgical distress found planning, instrumental support, humour and venting to be associated with increased distress, even though they are normally considered to be adaptive responses[217]. Acceptance was also found to be a risk factor for increased depressive symptoms and poorer QoL in HN cancer patients, but as the authors rightly point out, acceptance may be related to the extent of the cancer and resulting symptoms, for which no adjustment was made. Due to the broad range of categories and mixed findings, a full literature review is beyond the scope of this thesis, and in this study coping was included as an exploratory variable. There are many possible ways of measuring coping, the brief COPE[194] was chosen as it is widely used in cancer studies as well as in non

cancer groups and includes a broad range of conceptually different types of coping. The COPE allows for us to test the broad range and if a pattern emerges the types of coping could be appropriately interpreted under more general categories, such as problem or emotion focused[218].

7.1.6 Limitations and conclusions

In summary, this chapter focuses on the relationship between a group of well founded risk factors for development of a DE in the general population (CT, NE, LE and PH depression) and depression and QoL in cancer patients. Despite the strong association between CT, LE, NE, PH depression and coping and DDs in the general population, there have been few studies investigating these factors with respect to risk of depression in CR or HN cancer patients, which is the focus of this study. There are some limitations to the study, such as the use of self report questionnaires (see general methods, section 2.6). Interviews were considered unsuitable due to the extra burden on the patients and prospective measures are not available.

Childhood trauma, LE, NE and PH depression would all be expected to be associated with increased depressive symptoms, risk of DE6 and poorer QoL. There is a high possibility of covariation between the investigated variables as demonstrated by Kendler's model[62], which is discussed in chapters 9 and 10. No specific hypotheses for coping have been made and only patterns of associations are reported.

7.2 Results

The findings for each variable are presented in turn and follow the same structure i.e. starting with depressive symptoms as a dependent variable at baseline (T1), then at each prospective study wave (T3 to T5), supplemented by longitudinal analyses to look at time interactions and finally the risk of a DE. Quality of life

findings are presented in a similar manner. In all the analyses, the results for CR then HN patients are shown for each analysis unless the groups were combined.

7.2.1 Childhood trauma

7.2.1.1 Descriptives

Variable	CR patients		HN patients		General population[189, 219]	Significance
	N	Mean (sd)	N	Mean (sd)		
SA	**20**	**4.80 (1.15)**	**34**	**7.12 (4.79)**	**5-9**	***z=1.93, p=0.05***
PA	**20**	**4.95 (0.83)**	**34**	**7.35 (4.15)**	**6-8**	***z=3.04, p=0.002***
EA	**20**	**5.85 (2.39)**	**34**	**8.85 (4.98)**	**6-7**	***z=2.49, p=0.01***
PN	20	7.75 (3.48)	34	7.77 (3.60)	6-7	*z=0.69, p=0.49*
EN	20	11.10 (6.98)	34	11.65 (5.74)	7-10	*z=0.15, p=0.89*
Total	20	34.45 (7.49)	34	42.74 (17.53)	31-40	*z=-1.65, =0.10*

Table 7.1: Level of early life stress as indicated on the CTQ. SA= sexual abuse; PA=physical abuse; EA=emotional abuse; PN=physical neglect; EN=emotional neglect.

Even though the total scores were not significantly different, as can be seen in table 7.1 there was a higher level of abuse in the HN group compared to the CR group. Whilst the total difference was not significant, the results were still stratified as there was a different distribution of abuse in the two groups.

Sixty percent of CR patients and 44% of HN patients scored more than one on the denial score of the CTQ, indicating that this proportion of patients may be minimising any negative memories. There was a strong negative relationship between denial score and total score *[N=54 ß(CI)=-5.92 (-8.45 to -3.39) p<0.0005]*. Emotional abuse and neglect were also closely associated with minimisation.

7.2.1.2 Depression findings

There was no association between CT and depressive symptoms at T1 in CR patients *[p=0.403]*. However, there was a strong positive association between CT and HADS-D in HN patients *[N=32, ß(CI)=0.07 (0.03 to 0.11) p=0.001]*.

There was a strong positive association between CT and depressive symptoms at T3 in CR and HN patients *[CR:N=20, ß(CI)=0.27 (0.13 to 0.41) p=0.001; HN:N=31, ß(CI)=0.07 (0.00 to 0.15) p=0.041]*.

There was a positive association between CT and T4 HADS-D in CR patients, but only a trend in HN patients *[CR:N=19, ß(CI)=0.41 (0.27 to 0.55) p<0.0005; HN:N=34, ß(CI)=0.06 (0.01 to 0.13) p=0.097]*.

There was a positive association between CT and T5 HADS-D in both CR and HN patients *[CR:N=18, ß(CI)=0.35 (0.12 to 0.57) p=0.005; HN:N=33, ß(CI)=0.08 (0.02 to 0.15) p=0.017]*.

Consistent with the above analyses, there was an association between CT and HADS-D overall in both patient groups. However, when a time interaction was added to the model, the association became non significant in the CR group; however, there was a significant CT by time interaction at T4 *[p=0.038]*, and there was a trend towards a significant CT by time interaction at T5 *[p=0.096]*. In the HN group the main effect of CT remained significant *[N=34 β(CI)=0.07 (0.04 to 0.11), p<0.0005*], but there were no time interactions. Figure 7.1 shows the relationship between CT and depressive symptoms at each time wave in CR patients.

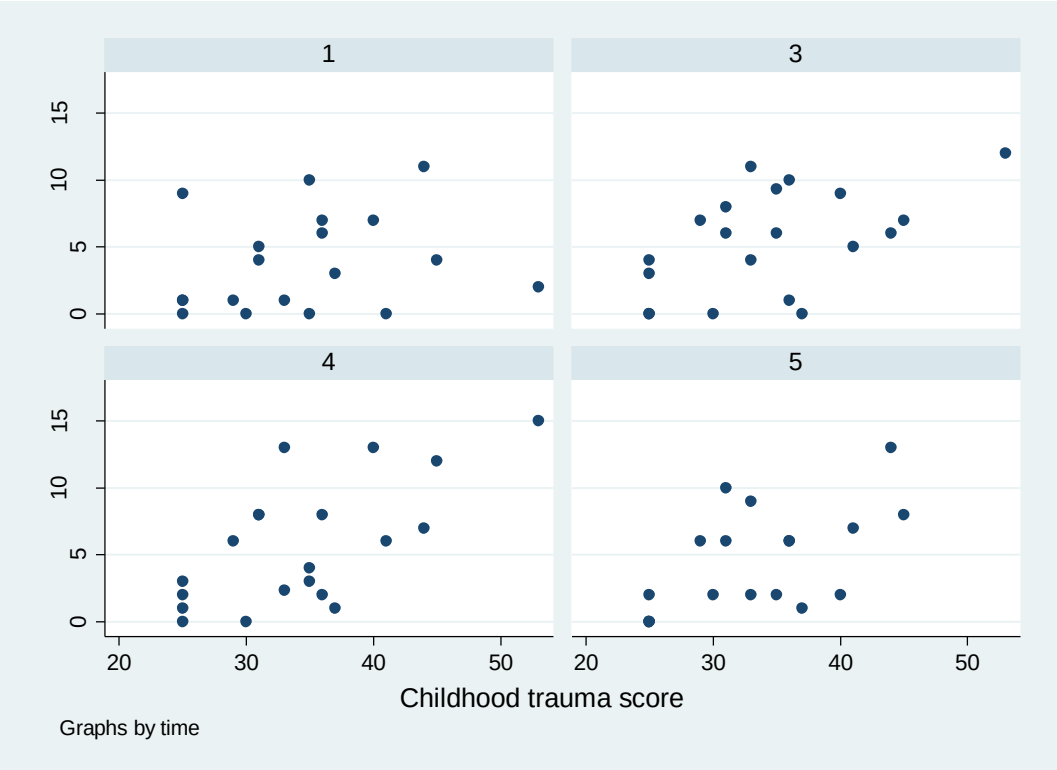


Figure 7.1: Scatter plot between CT and depressive symptoms at each time point in CR patients.

There was no evidence to suggest an association between CT and increased risk of a DE6 in a combined analysis.

7.2.1.3 Quality of life findings

There was no evidence to suggest an association between CT and poorer QoL in either patient group at T1 *[CR: p=0.094; HN: p=0.191]*.

At T3 there was evidence of an association between CT and poorer QoL in CR and HN patients *[CR:N=20, ß(CI)=-1.74 (-3.25 to -0.24) p=0.026; HN:N=31, ß(CI)=-0.42 (-0.74 to -0.10) p=0.012]*.

At T4 there was evidence towards an association between CT and poorer QoL in CR patients, but not HN patients, but there was a trend in HN patients *[CR:N=19, ß(CI)=-1.37 (-2.73 to -0.01) p=0.049; HN:N=34, ß(CI)=-0.33 (-0.72 to -0.05) p=0.082]*.

There was evidence towards an association between CT and poorer QoL in CR patients at T5, but not HN patients *[CR:N=17, ß(CI)=-2.36 (-4.04 to -0.69) p=0.009; HN:N=33, ß(CI)=0.09 (-0.40 to 0.57) p=0.720]*.

Overall, there was a negative association between CT and QoL in CR patients, but not in HN patients *[CR:N=74(20), ß(CI)=-1.65 (-2.57 to -0.72) p<0.0005; HN:N=129(34), ß(CI)=-0.25(-0.57 to 0.07) p=0.132]*. There was no interaction in either group.

7.2.2 Summary

Childhood trauma was associated with increased depressive symptoms in both CR and HN patient groups. This effect was more pronounced in the CR group after treatment, especially at T4, whereas in HN patients the effect is consistent throughout. There was no association between CT and risk of DE6. Also, CT was only associated with poorer QoL in the CR group.

7.2.3 Neuroticism results

7.2.3.1 Prevalence

There were no differences in the levels of NE in the two cancer groups (see table 7.2) and levels are representative of the general population (mean=8.8, sd=5.0)[208]. There was no association between the lie scale and NE score.

CR		HN		*Significance*
N	Mean (sd)	N	Mean (sd)	
41	8.76 (5.08)	22	7.95 (5.30)	*t(61)=0.59, p=0.56*

Table 7.2: Means and sd of levels of NE by cancer group.

7.2.3.2 Depression findings

At T1 there was a weak trend towards an association between NE and HADS-D in CR patients *[p=0.167]*. Neuroticism was positively associated with depressive symptoms at T1 in HN patients. As the association in CR patients was probably insignificant due to smaller numbers, both groups were combined and the association found in the HN group remained *[N=59, ß(CI)=0.25 (0.13 to 0.38) p<0.0005]* (figure 7.2).

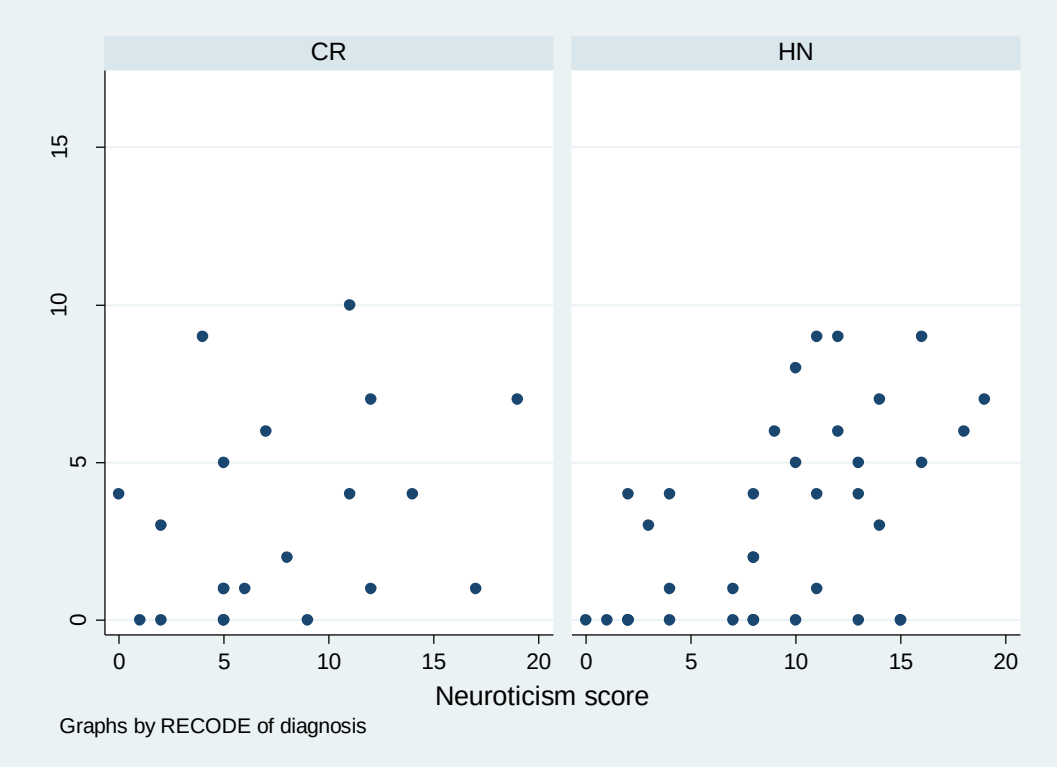


Figure 7.2: Correlation between depressive symptoms at T1 and NE by type of cancer.

Neuroticism was associated with HADS-D at T3 in both CR and HN patients. Similarly, NE was associated with HADS-D at T4, T5 and overall in CR and HN patients (see table 7.3).

	Time	N	ß(CI)	*P value*
CR	*1*	*21*	*0.18 (-0.08 to 0.43)*	*0.167*
	3	*21*	*0.052 (0.31 to 0.75)*	*<0.0005*
	4	*21*	*0.59 (0.34 to 0.85)*	*<0.0005*
	5	*18*	*0.31 (0.00 to 0.62)*	*=0.048*
Overall		*22*	*0.40 (0.22 to 0.58)*	*<0.0005*
HN	*1*	*38*	*0.31 (0.17 to 0.46)*	*<0.0005*
	3	*38*	*0.29 (0.06 to 0.51)*	*0.051*
	4	*41*	*0.48 (0.30 to 0.65)*	*<0.0005*
	5	*39*	*0.32 (0.12 to 0.51)*	*0.002*
Overall		*41*	*0.35 (0.21 to 0.48)*	*<0.0005*

Table 7.3: Coefficients (CI) and p values of association between NE and HADS-D.

There was an interaction over time in the CR patient group; patients with high levels of NE showed increased depressive symptoms at T3 *[p=0.008]* and T4 *[p<0.0005],* but the main effect of NE was reduced to a trend after including the interaction term.

There was a weak interaction in HN cancer patients at T4 *[p=0.054]* again with patients with high levels of NE showing higher levels of depressive symptoms. In this case the main effect of NE was still highly significant.

As the two groups showed similar results, the patients were pooled and analysed altogether. These results indicated a positive association between NE and depressive symptoms overall and a further increase in depressive symptoms at T4 in those with higher levels of NE *[N=237(63), ß(CI)=0.27 (0.14 to 0.39) p<0.0005, T4 interaction term p=0.0001]*.

High levels of NE were associated with increased risk of a DE6 when analysing all patients as one group *[N=60, OR(CI)=1.45(1.20-1.74) p<0.0005]*.

7.2.3.3 QoL findings

There was a trend towards an association between NE and poorer QoL in CR patients *[p=0.109]* and a significant association in HN patients *[N=37, ß(CI)=-1.14 (-2.06 to -0.23) p=0.016]*. Thus, as with the results for T1 HADS-D, groups were combined *[N=57, ß(CI)=-1.23 (-2.18 to -0.27) p=0.013]*.

There was a significant association between NE and decreased QoL at T3 in CR patients *[N=21, ß(CI)=-2.09 (-3.85 to -0.32) p=0.023]* and no significant association in HN patients *[p=0.240]*.

Similar to baseline, there was a trend towards an association between NE and poorer QoL at T4 in CR patients *[p=0.108]* and a significant association in HN patients *[N=41, ß(CI)=-2.00 (-3.15 to -0.84) p=0.001]*. Thus, the groups were combined *[N=62, ß(CI)=-1.76 (-2.68 to -0.83) p<0.0005]*, which showed a significant association between NE and poorer QoL at T4.

There was a trend towards a significant association between NE and poorer QoL at T5 in CR patients *[p=0.140]*. However, there was no association between NE and poorer QoL at T5 in HN patients *[p=0.918]*.

There was an overall association between increased levels of NE and poorer QoL in both patient groups (though weaker in HN patients) *[CR:N=79(22), ß(CI)=-1.67 (-2.87 to -0.48) p=0.006; HN:N=155(41), ß(CI)=-0.93 (-1.90 to 0.03) p=0.058]*. There were no time interactions.

7.2.3.4 Summary

Neuroticism is a strong risk factor for increased depressive symptoms (and more so at T4) and likelihood of a DE after a cancer diagnosis. Neuroticism is also a risk

factor for poorer QoL, but the effect is greater in CR patients and is less pronounced by T5 in both patient groups.

7.2.4 Life events results

7.2.4.1 Prevalence

Variable	CR patients		HN patients		*Significance*
	N	Mean (sd)	N	Mean (sd)	
Stressful life events T3	27	1.96 (1.79)	45	2.58 (1.62)	*z=1.71, p=0.09*
Stressful life events T5	23	1.26 (1.45)	40	1.3 (1.15)	*z=1.41, p=0.16*

Table 7.4: Mean (sd) number of stressful LE by cancer group.

Table 7.4 shows the mean number of LE by cancer group. Only findings for stressful LE at T3 are reported as the BLEQ scores at T5 were not associated with any of the dependent variables. Also, despite three possible methods of scoring the BLEQ, only the findings for the number of stressful LE are reported because the other methods generated similar results, but with slightly smaller effect sizes. (As stated in chapter 5, the other methods were either 1) including only moderate or very bad LE or 2) treating the questionnaire as a scale.)

7.2.4.2 Depression findings

Life events were positively associated with depressive symptoms at T1 in HN patients, but not CR patients. As there was a trend in CR patients *[p=0.152],* the two groups were combined and the association was significant (see table 7.5).

Life events were positively associated with depressive symptoms at T3, T4 and T5 in HN patients and a trend was seen in CR patients for each time point *[p=0.158, 0.073 and 0.063 respectively],* thus the two groups were combined (see table 7.5).

	Time	N	ß(CI)	P value
HN	*1*	*42*	*0.80 (0.10 to 1.49)*	*0.025*
	3	*44*	*1.75 (1.34 to 2.16)*	*<0.0005*
	4	*41*	*0.48 (0.30 to 0.65)*	*<0.0005*
	5	*39*	*1.35 (0.61 to 2.10)*	*0.001*
CR and HN	*1*	*68*	*0.63 (0.16 to 1.10)*	*0.010*
	3	*69*	*1.23 (0.75 to 1.70)*	*<0.0005*
	4	*62*	*0.51 (0.37 to 0.65)*	*<0.0005*
	5	*61*	*0.99 (0.46 to 1.52)*	*<0.0005*

Table 7.5: Coefficients (CI) and p values of association between LE and HADS-D

There was a significant association of LE at T3 with increased depressive symptoms overall in CR patients and HN patients *[CR:N=27, ß(CI)=0.60 (0.10 to 1.10) p=0.020; HN: N=45, ß(CI)=1.24 (0.76 to 1.72) p<0.0005]*. There was no significant interaction with time in the CR group. However, in the HN group there was a significant interaction between HADS-D and number of LE at T3 *[p=0.0002]* and the main effect of LE remained in HN patients *[N=165(45), ß(CI)=0.73 (0.04 to 1.42) p=0.038]*. This indicated that those who reported more life events at T3 tended to have higher levels of depressive symptoms overall and even more so at T3 (the same time the BLEQ was completed). See figure 7.3 for an illustrative graph of all groups HADS-D scores over time, split by median BLEQ score.

LE at T3 were associated with increased risk of a DE6 (when analysing all patients as one group) *[N=63, OR(CI)=2.53 (1.60-4.00) p=0.005]*.

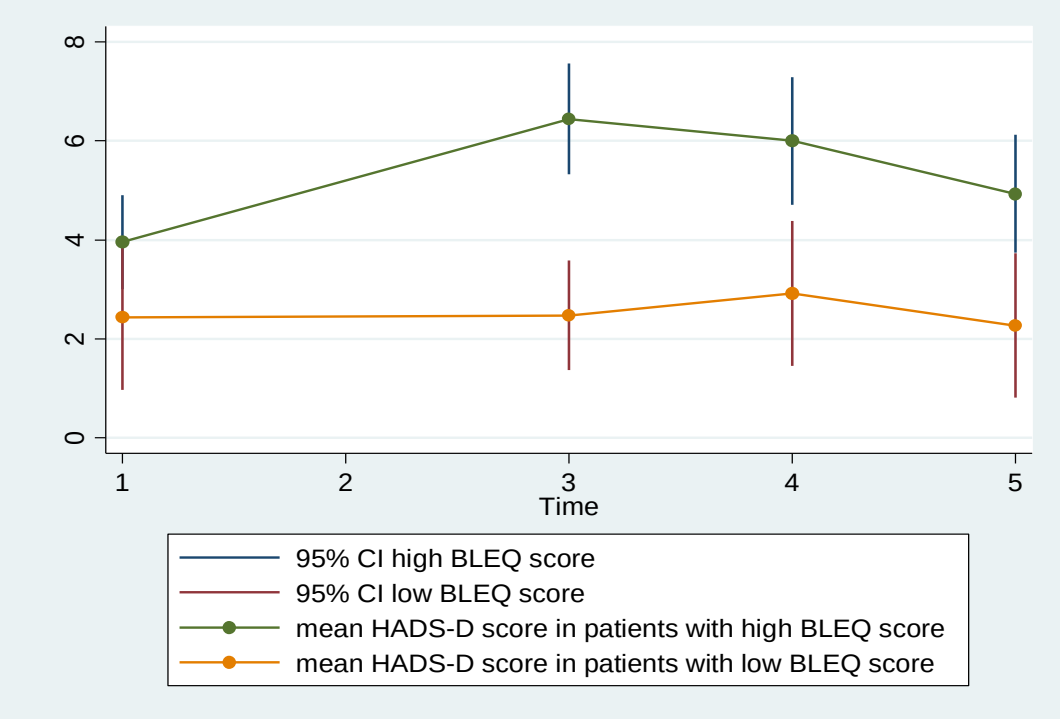


Figure 7.3: Graph of mean HADS-D scores by BLEQ median split. N=72.

7.2.4.3 Quality of life findings

There was no association between LE and QoL at baseline in CR patients *[p=0.711]*. There was a strong association in HN patients *[N=41, ß(CI)=-6.04 (-10.32 to -1.76) p=0.007]*.

There was no association between LE and QoL at T3 in CR patients *[p=0.232]*. There was a strong association in HN patients *[N=44, ß(CI)=-7.72 (-11.07 to -4.36), p<0.0005]*.

There was a significant negative association between LE and QoL at T4 in both sets of patients *[CR:21, ß(CI)=-2.09 (-3.85 to -0.32) p=0.023; HN:N=41, ß(CI)=-2.00 (-3.15 to -0.84) p=0.001]*.

There was no significant association between LE and QoL at T5 in either patient group *[combined group p=0.192]*.

There was a trend of an association overall in CR patients *[p=0.129]* and a significant negative association in HN patients and combined *[N=162(45), ß(CI)=-6.30 (-9.43 to -3.17) p<0.0005; All:N=257(72), ß(CI)=-4.59 (-7.13 to -2.05) p<0.0005]*. There was no interaction with time.

7.2.4.4 Summary

Life events at T3 were associated with depressive symptoms in both patient groups. Life events were also associated with decreased QoL in HN patients and to some extent in CR patients, but the effect was no longer significant at six months post treatment.

7.2.5 PH depression results

As can be seen in table 7.6 only a small number of CR patients had a PH of depression. These analyses were always combined. There appears to be a higher proportion of DEs in the HN group, but this difference was not significant.

7.2.5.1 Prevalence

SCAN diagnosis	CR		HN		Significance
	N (%)		N (%)		
PH depression					
N	26		39		$\chi^2(1)=0.65, p=0.42$
Y	3	**(10.34)**	8	**(17.02)**	
DE6					
N	21		33		$\chi^2(1)=0.82, p=0.37$
Y	3	**(12.50)**	9	**(21.43)**	
PH of anxiety					
N	26		43		$\chi^2(1)=0.35, p=0.55$
Y	3	**(10.34)**	3	**(6.52)**	
Anxiety within 6 months					
N	21		39		$\chi^2(1)=0.53, p=0.47$
Y	3	**(12.50)**	3	**(7.14)**	

Table 7.6: Prevalence of depressive or anxiety disorder by diagnosis.

7.2.5.2 Depression findings

There were higher levels depressive symptoms at all time points in patients with a PH of depression (see table 7.7).

Time	N	ß(CI)	*P value*
1	*72*	*2.27 (0.12 to 4.41)*	*0.039*
3	*67*	*3.18 (0.83 to 5.53)*	*0.009*
4	*65*	*4.97 (2.01 to 7.92)*	*0.001*
5	*61*	*4.32 (0.97 to 7.67)*	*0.012*

Table 7.7: Coefficients (CI) for association between PH depression and HADS-D.

There was a significant association overall between PH depression and increased depressive symptoms *[N=257(72), ß(CI)=2.53 (0.48 to 4.58) p=0.015]*. There was also a significant interaction at T4 *[p=0.009]* indicating that those with a PH depression had higher levels of depressive symptoms throughout the study and higher still at T4 (see figure 7.4).

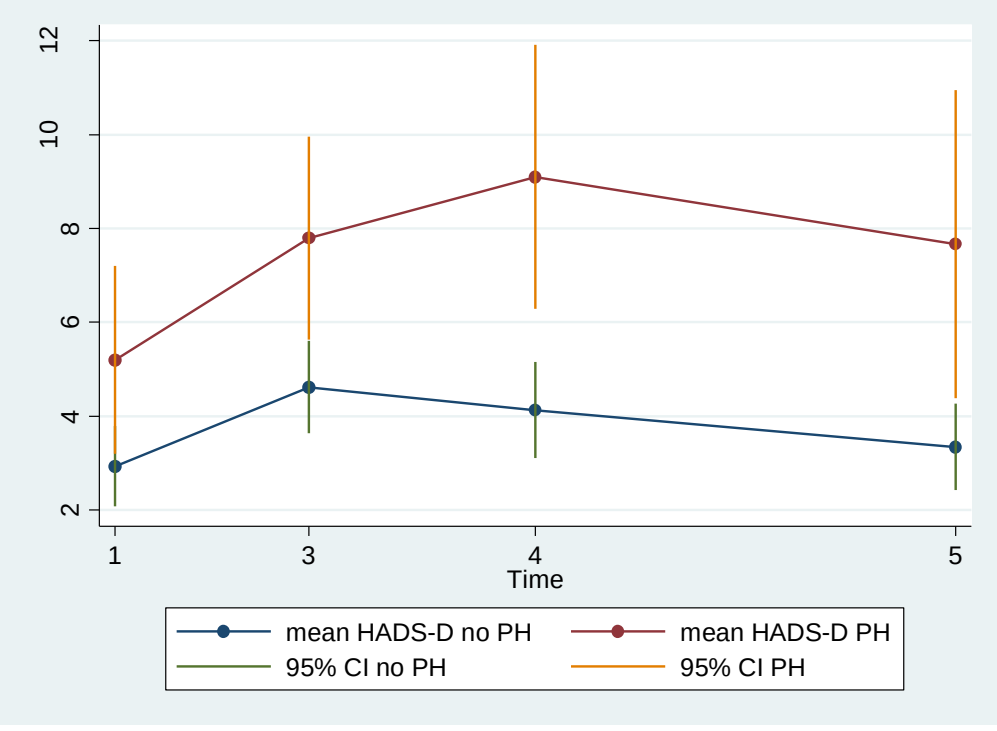


Figure 7.4: Mean HADS-D scores over time in all patients by those with and without a PH of a DD (N=76).

Patients with a PH depression were at 50x greater odds of a DE6. The confidence intervals for this result are very high, indicating decreased reliability *[N=65, OR(CI)=51.00 (7.87 to 330.32) p<0.0005]*.

7.2.5.3 QoL findings

There was a significant association between PH depression and poorer QoL at baseline (see table 7.8).

Time	N	ß(CI)	*P value*
1	*70*	*-15.83 (-30.59 to -1.08)*	*0.036*
3	*67*	*-14.77 (-25.91 to -3.62),*	*0.010*
4	*63*	*-14.66 (-24.18 to -5.14)*	*0.003*
5	*59*	*2.80 (-14.02 to 19.61)*	*0.740*

Table 7.8: Coefficients (CI) for association between PH depression and global QoL.

There was a significant association between PH depression and reduced QoL overall *[N=259(76), ß(CI)=-12.38 (-21.29 to -3.48) p=0.006]*, but no interaction with time (although a trend towards an interaction at T5 *[p=0.110]*).

7.2.5.4 Summary

Past history of depression was associated with increased depressive symptoms throughout the study period and more so at T4. Past history of depression was also associated with an increased risk of a DE6 and poorer QoL, but it was no longer related to QoL at T5.

7.2.6 Coping results

As there were no specific hypotheses involving coping, this was an exploratory investigation. Thus, in order to ensure cautious interpretation of the results, no single findings will be reported but just general themes.

7.2.6.1 Prevalence

There were no differences in the types of coping used in either cancer group (see table 7.9).

Variable	CR		HN	
	N	Mean (sd)	N	Mean (sd)
Self distraction	22	2.91 (2.33)	40	2.85 (1.92)
Active	22	3.91 (2.27)	40	4.15 (1.99)
Denial	22	1.65 (2.17)	40	1.18 (1.81)
Substance use	22	0.57 (1.56)	40	0.70 (1.29)
Use of emotional support	22	4.35 (2.17)	40	4.03 (2.09)
Use of instrumental support	22	2.48 (2.56)	40	2.10 (1.89)
Behavioural disengagement	22	1.30 (1.87)	40	0.88 (1.67)
Venting	22	1.61 (1.90)	40	0.98 (1.42)
Positive reframing	22	3.87 (2.40)	40	3.85 (1.87)
Planning	22	3.52 (2.41)	40	3.43 (2.31)
Humour	22	2.35 (2.10)	40	2.10 (2.35)
Acceptance	22	4.57 (1.85)	40	4.63 (1.48)
Religious coping	22	2.00 (2.22)	40	1.55 (1.93)
Self-blame	22	0.74 (1.18)	40	1.00 (1.47)

Table 7.9: Coping strategies by cancer group.

7.2.6.2 Results

There were very few consistent findings with regard to any of the coping strategies and HADS-D or QoL scores that were considered robust enough to report. However, there was an inverse association between humour and HADS-D at T4 in

both CR and HN patients *[CR:N=22, ß(CI)=-0.76 (-1.53 to 0.00) p=0.004; HN:N=40 ß(CI)=-0.46 (-0.89 to -0.04) p=0.033]*. This effect was only found at T4 and did not translate into improved QoL.

7.3 Discussion

Overall, the findings supported the hypotheses under study and were consistent with past research: CT, NE, LE and PH depression were all associated with increased depressive symptoms and poorer QoL. Neuroticism, LE and PH depression were also associated with increased risk of a DE6. However, there were also a few surprising findings (for instance, CT was not associated with an increased risk of a DE6). Also, more detailed analyses suggest these relationships are more complex and the results for each variable are discussed in more detail below.

7.3.1 Childhood Trauma

The levels of CT were significantly higher in HN patients compared to the CR patients. When compared to the general population, levels of CT appear to be slightly higher in HN patients and slightly lower in CR patients. This is an intriguing finding, and may be spurious due to the small sample size. It was considered that CT could be associated with increased levels of smoking and alcohol consumption, but the association remained when using multivariate regression (results not shown). It is also possible that HN cancer is associated with increased levels of sexual abuse, since sexual abuse is associated with increased risk of sexually transmitted diseases in childhood[220]. Therefore there is a higher level of HPV infection from a younger age in those with high levels of sexual abuse. HPV has recently been identified as an important risk factor for oral cancer[35, 221]. However this explanation is very speculative as there is limited research in this area.

There was an association between CT and depressive symptoms and QoL in both CR and HN patients, but the relationship differs between the two diagnoses. The

association between CT and HADS-D in the CR group was only apparent at T4 indicating that the effect in CR patients is only apparent at periods where there is an overall trend towards low mood, whereas the association between CT and HADS-D in HN patients remained consistent throughout the study period. This may be due to a threshold effect in the HN group due to the increased range of values in that sample. However, the CR finding may also be due to the timing of the questionnaires, which is discussed in the limitations (section 7.3.6). Surprisingly, there was no association between CT and QoL in the HN group but there was an association in the CR group, the reasons for this are not clear and may be due to the different spread of CT in the two groups. This may be due to 1) stronger relationships between certain types of trauma and QoL, which are more apparent in the CR group; 2) cancer related factors confounding the relationship between CT and QoL in either cancer group, or most likely 3) a lack of power leading to an influence of both factors which has affected the reliability of the results.

Despite the emerging theme of an association between CT and depressive symptoms, CT did not significantly increase the risk of DE6. Again, this was an unexpected finding and it is possible that only certain types of CT are associated with increased risk of a DE, in which case the decision to analyse total CT will have obscured that result. However, it is more likely that the study is simply underpowered to detect this, especially given the relatively short period of time of follow up for development of a DE and the number of other variables to be considered. Finally, to be able to interpret findings more fully, a qualitative approach may be helpful. For instance, one patient reported harrowing amounts of CT and reported never having experienced a DE either before or after his cancer diagnosis. However, whilst this patient was not overtly miserable, neither was he overtly happy; he showed a generally quite restricted affective range and merely agreed that his ‘life had been tough’. Thus, whilst he had never experienced a period where his mood was noticeably lower, he appeared to have lower than average mood throughout our engagements. When this patient was excluded from

the analysis there was a trend towards CT and increased risk of a DE6, but it still was not significant. This is obviously a single observation, but it helps to illustrate the complexity of the relationship between risk factors and depressive illness. Further quantitative studies may benefit from conducting some interviews with patients, as a qualitative approach could add depth to the findings.

In summary, there was an overall association between CT and depressive symptoms in both cancer groups, but the timing and extent of the relationship varied and CT did not increase the risk of a DE6. Also, the relationship between CT and QoL was only apparent in CR patients, indicating that the effect of CT on depressive symptoms did not extend to QoL. Further work with more precise measures and larger samples should be able to test whether the unexpected findings are real effects and if they are related to type of trauma.

7.3.2 Neuroticism

Neuroticism was strongly associated with depressive symptoms, risk of DE6 and poorer QoL in both CR and HN patients, supporting past studies. The relationship between NE and depressive symptoms was most pronounced at T4 and less so by T5. It is possible that the increase at T4 is because that is the time point when cancer patients are most vulnerable to low mood after a cancer diagnosis[146], but it may also be related to the timing of the questionnaires.

7.3.3 Stressful Life Events

Number of LE in the past six months, assessed one month after treatment, was associated with increased depressive symptoms and increased risk of a DE6 in both patient groups, supporting past findings. The association was weaker in the CR group, but that is most likely to be due to lower power. There was no association between number of LE at six months after treatment with depressive

symptomatology or QoL at any time point, suggesting only events around the time of the diagnosis were associated with depression and poorer QoL. However, again there is a possibility that this may have been confounded by the timing of the questionnaires, which is discussed in the limitations (section 7.3.6). The association between LE and QoL appears to be stronger in the HN patients compared to the CR patients. Nevertheless, there is no evidence of an association at six months in either patient group. In summary, there was a strong association between number of LE at the time of cancer diagnosis and depressive symptoms, risk of a DE6 and poorer QoL. This is an important finding which clinicians need to be aware of, which is discussed in more detail in the general discussion.

7.3.4 PH depression

Past history of depression was associated with increased depressive symptoms at all time points, particularly at three months after diagnosis, compared to those without a PH. The increased association at three months suggests that PH of depression is related to an underlying vulnerability to low mood and has a further impact on low mood during periods after a cancer diagnosis which are associated with increased low mood in all patients. Past history of depression was also associated with poorer QoL, but this was no longer significant by six months after treatment. There appear to be no past studies on the relationship between PH depression and QoL at six months after treatment. It is possible that the relationship between PH depression and depressive symptoms does not result in poorer QoL beyond six months after treatment, implying the relationship between PH of depression is related to acute stress levels. However, it is not possible to test this using these data. Past history of depression was also associated with increased risk of a DE6, similar to previous reports on breast cancer patients[222]. However, the confidence intervals for the association were very high, suggesting that it is a large effect but that the data set is underpowered and further studies with larger samples would be required to test this hypothesis.

7.3.5 Coping

The analysis revealed very few consistent patterns between coping and depressive symptoms or QoL and no coping methods appeared to increase or decrease the risk of a DE6. However, using humour to help cope with the cancer was associated with decreased depressive symptoms three months after treatment in both sets of cancer patients. A similar protective effect of humour at that time has previously been reported in a group of breast cancer patients[223]. On the other hand, a study in a large sample of 1800 CR patients six months after their diagnosis found no association with distress or QoL and coping with humour[224]. This suggests that perhaps the beneficial effect of coping is only apparent at times of greater distress. Humour has also been associated with poorer QoL in HN patients eight years after their diagnosis[212]. However this is a long time to test for an association as coping strategies change over time[223].

7.3.6 Limitations

The lack of a control condition prevents any interpretation of whether the risk factors confer a greater risk of a DE in cancer patients compared to healthy controls, or those with other medical conditions. The sample is also very small, so there is an increased risk of false negative findings. This is especially the case since the sample has been stratified by diagnosis. Whilst normally samples are not stratified unless there is a significant interaction, due to the small sample sizes, even quite large interactions between the two samples are likely to be statistically non-significant. However, as the CT findings suggest, the relationships vary between the samples, so stratification was a necessary precaution. The difference in effects also suggests that it might be worth analysing the relationship between the different subtypes of CT and depressive symptoms, as the differentiation may be more related to different trauma distributions in the two cancer populations rather than the diagnosis. However, there would not be enough power to conduct these analyses in this sample.

The study is largely dependent on retrospective self report questionnaires which could be biased by current mood and social desirability[167, 168]. This is especially concerning given the increased association between CT and NE and depressive symptoms at T4, which is when more patients completed that questionnaire. Similarly, LE are most significantly associated with depressive symptoms at T3, at the time when patients completed the BLEQ.

With respect to the CT finding, a review of studies investigating the reliability of retrospective CT reports found that most people tend to minimise childhood stress[206], and there was evidence of minimisation in this sample which was associated with lower levels of emotional abuse and neglect. However, it would be hard to prove that the scale is a genuine marker of denial. Despite what the minimisation scale implies, it is plausible that some adults truly did enjoy their childhood and appreciated it even when they were a child. The more problematic issue in the CT finding is whether there is an effect of low mood on reported levels. As stated in the introduction, low mood is associated with a negative memory bias, which would lead to reporting more negative memories. A large Swedish study including over 2,000 participants found that 14% of the participants who reported ELS at first completion of the questionnaire did not report any three years later during a repeated assessment[200]. Although 14% in such a large sample may not obscure the true relationship, such variation in this study would have a significant effect on the results.

With respect to the association between LE and depressive symptoms, whilst LE reporting should be objective, past studies suggest that this is not always the case[225]. The greatest association between LE and depressive symptoms was at one month post surgery when patients completed the BLEQ. Some studies have found an increase in participant reported LE after a negative mood induction, compared to a positive or neutral mood induction[225] suggesting the number of reported LE may have been affected by a retrospective response bias. However,

more naturalistic studies have not found this to be the case[226]. It is unlikely, but also possible, that those with higher levels of depressive symptoms, if chronic, exaggerate the extent or number of stressful LE, thus leading the confidant to also over-report the number of LE.

There is also an increased association between NE and depressive symptoms at T4. Whilst some have found that NE levels were stable in a small sample of HN cancer patients who were tested for NE levels at the time of diagnosis and four years later[227], many other studies report an influence of current mood[228]. Some go as far as to describe NE as a proxy measure of a person's level of distress with test retest reliability diminishing rapidly over longer periods of time[228]. This suggests that whilst NE is evidently predictive of lower mood, it may be no more informative than using a HADS at baseline.

Despite the findings of CT, LE and NE suggesting that the association may be at least in part due to a recall bias, the association between PH depression and depressive symptoms is also greatest at T4. Clinically assessed PH depression should be less biased by current mood symptoms, especially as it was assessed after T4. Although PH depression is also likely to be associated with CT, LE and NE, this finding does provide some evidence towards a true effect of raised association between the group of psychological risk factors and depressive symptoms at T4. The issue of covariance is addressed in chapter 9.

In total, there is evidence to suggest that the effect of CT, NE, LE and possibly even PH depression could be, at least in part, due to biases in self report questionnaires. The level of association between HADS scores over time indicates that any biases at T4 will also spread to other time points. No association was found between many of the psychological variables and depressive symptoms at T3 when adjusting for depressive symptoms at T4, but this could also be due to over adjustment (analyses not shown).

7.3.7 Conclusions

These results show a relationship between CT, NE, LE and PH depression and increased depressive symptoms, poorer QoL and risk of a DE6 in CR and HN cancer patients. Thus, risk factors applicable to the general population also increase the risk of depression in cancer patients. The prospective nature of the study has allowed in-depth analyses which have shown there are some differences in the relationships between the two cancer diagnoses and over time. Many of these relationships appear strongest three months after treatment finishes and are weakest or do not persist by six months, which may be an artefact of the protocol rather than a true effect. On the other hand, it is also feasible that, as between one and four months appears to be when cancer patients are most vulnerable to lower mood, the investigated variables genuinely have a greater effect at those times (as indicated by the findings in the previous chapter). It is therefore of interest to compare these findings to those for the physiological markers and whether they show a greater effect at the same time points (see next chapter). There is also the possibility of covariance between each of the investigated factors and the relative strengths of CT, NE, LE and PH depression which is investigated in later chapters.

In summary, this chapter reports the results of the investigated psychological markers for depression and poorer QoL in cancer patients up to six months after their diagnosis. This chapter addressed the first hypothesis of the study and found that a PH depression was associated with increased depressive symptoms, poorer QoL and an increased risk of a DE6. These results also addressed parts of the third aim of the thesis: exploring associations between other explanatory factors on depressive symptomatology and QoL. The other factors, CT, NE and LE were all found to be risk factors for increased depressive symptoms, poorer QoL and risk of a DE. This shows that much of a cancer patient's QoL is associated with non cancer related variables, though clearly cancer related symptoms are also associated with depressive symptoms and overall QoL, as illustrated in chapter 5. The next chapter investigates potential physiological markers.

8 Role of physiological factors

The previous results chapters described the sample and reported on the association between the psychological factors and depressive symptoms and QoL. This chapter investigates associations between physiological variables, cortisol and inflammation, and prospective measures of QoL in cancer patients.

The chapter aims to address the third and fourth hypothesis included in the aims of the thesis: iii) that patients with increased HPAA activity will show increased depressive symptoms and iv) that patients with increased cytokine levels will show more depressive symptoms. As with previous chapters, a literature review precedes the results comprising a brief overview of current understanding of the relationship between cortisol and cytokines and depression in cancer patients. The first question addressed is why increased levels of inflammation might be especially relevant to cancer treatment outcome, including possible increased mortality. Whilst mortality is not being investigated in this thesis, it is important to understand the possible implications of comorbid depression and raised cytokines with respect to tumour growth to understand the rationale behind this study. Secondly, the literature on cytokines and depression is revisited focusing on the salient points regarding each of the cytokines and more technical details which underlie the hypotheses for this section. The section concludes with a discussion of the results.

8.1 Background

8.1.1 Cytokines, cancer and progression

Cytokines are messenger molecules that form part of the immune response (see section 1.2.4.2). It is now well established that there is a large inflammatory component to tumours and cytokines are known to be both protective and damaging to malignant cells. Whether they help or hinder cancer growth and spread appears to be related, not only to the type and development stage of the tumour, but also to the level and length of exposure to cytokines. For example, reduction of cytokines can impede growth of some tumours, but promote the growth of others[145]. Also, TNF in high doses can help destroy a tumour, but low chronic doses are thought to promote tumour growth[229]. Mice deficient in IL1 or IL6 show resistance to experimental metastases[229].

The relationship between IL6 and CR cancer progression has been extensively investigated. A recent review[230] found that CR patients show higher levels of IL6 compared to healthy controls. Further studies reported positive associations between IL6 and tumour stage, size and decreased survival in CR patients[230]. Although not all studies show an association between increased IL6 levels and decreased survival (e.g. Komoda *et al*., 1998[231]), four out of five of the reviewed studies showed a positive effect[230]. Moreover, a recent study[232] found that IL6 was associated with decreased survival even after adjusting for TNM stage, though the methods or full results for the multivariate analyses were not included. IL6 has also been found to be associated with poorer physical function in older patients[233]. Less research has been carried out on other inflammatory markers; although studies have shown that increased CRP levels are also associated with shorter survival and recurrent disease[234]; though another study found that CRP was not an independent risk factor after adjusting for tumour stage[235]. Studies comparing levels of TNFα in CR patients compared to controls have found the levels to be below detection[236]. Conversely, those measuring stimulated TNFα levels found higher levels were associated with increased survival, and systemic TNFα

correlated with decreased malignant cell proliferation in CR cancer patients[237]. The same group found no correlation between IFNγ and patient survival although there was a weak trend towards a positive association between IFNγ and increased survival.

In vitro studies investigating proliferation and invasiveness of CR tumour cells have found that IL6 promotes growth of CR cancer cells in a dose dependent manner and increases their invasiveness[230]. In vitro studies have also found that incubation with TNFα and IL1ß, but not IL6, enhances tumour adhesions to mesothelial cells[238]. Similar to previously reported findings, showing IL1ß and TNFα increased adhesion of CR cancer cells to lung and umbilical endothelial cells, but no findings for IL6[239]. Pre incubation with cytokines did not enhance adhesion, but preincubation with IL1ß increased cell growth, whereas four days of preincubation with TNFα decreased cell growth[239].

In HN patients, in vivo studies have similarly shown higher serum levels of IL6 and that increased levels of IL6 and CRP are associated with more lymph node metastases[240]. CRP was also associated with poorer survival, but this was no longer significant when adjusting for cancer stage[240]. IL6 is also associated with decreased survival in HN cancer patients[241, 242] though no adjustments were made for cancer stage. Increased stimulated production of IL6 from monocytes has also been associated with decreased survival[243, 244].

In vitro IL6 studies have shown that HN tumour cells express higher levels of IL6 than normal cells[245] and that recombinant IL6 inhibits the proliferation of some (but not all) HN cancer cell lines, but increases invasion potential in all squamous cell lines[246, 247].

Taken together this implies a very complex relationship even between different types of cancer cells and individual cytokines. The in vitro studies suggest some cytokines can aid cancer growth and spread under certain conditions. However, as

cytokines rarely act alone, the in vitro studies are only informative when interpreted in the context of the prospective studies showing that increased inflammation tends to be associated with poorer prognosis.

There have also been some reports proposing a relationship between cortisol and cancer progression, as cortisol is reported to be associated with lowered immunity[248]. However, HPAA activity is reported to be enhanced by inflammation (see section 1.2.4.3), thus any findings between cortisol and cancer progression are likely to be confounded by the link between inflammation and cortisol. The nature of this link is further expanded on in the next chapter.

Finally, it is worth noting that there is also evidence to suggest that high levels of IL6 and CRP lead to increased all cause mortality in elderly women both with and without cancer[144]. In particular, there was no significant difference in mortality rates between the cancer patients and those without cancer; suggesting that inflammation may not be related to cancer specific mortality and different mechanisms may be at play[144]. However, there was no analysis of the same data to investigate the effect of inflammation on cancer specific mortality.

In summary, there is evidence for an association between increased inflammation and poorer prognosis in CR and HN cancer patients but the underlying mechanisms remain to be identified. Overall, it appears that increased inflammation in cancer patients is associated with decreased survival.

8.1.2 HPAA function and depression

As previously discussed (section 1.2.4.1) HPAA dysregulation is often found in patients with a DD. In healthy individuals, cortisol secretion follows a circadian rhythm, with high levels on waking followed by a further sharp rise (of about 50%[249]) then a gradual decline throughout the day with a nighttime nadir. Many patients suffering from a DD show an increase in daily mean cortisol levels, an

increased morning rise[81] and increased evening activation[82, 250, 251]. Steptoe and colleagues[252] (2008) also found that average cortisol levels were negatively associated with positive affect in a sample of almost 3000 participants. Stress is thought to be a major causal factor in the aetiology of DDs and the findings of increased morning rise in depressed patients similarly occur in healthy individuals who suffer from chronic stress[78, 109, 253]. Those with high levels of depressive symptoms have also shown similar patterns to chronically stressed individuals[254]. Increased cortisol has been reported in those that are vulnerable to depression, such as individuals who experienced CT[255], have a family history of DD[256] or show high levels of NE[115]. These findings support the hypothesis of a causal role of HPAA dysregulation in depression and suggest a possible underlying mechanism for the relationship between CT and increased risk of a DD, which is elaborated in the next chapter. Increased cortisol has also been shown to be associated with CNS abnormalities related to depression, such as deficient monoamine function[257, 258]. As a result of all of these findings, HPAA dysregulation has been suggested as a major risk factor for development of a DD[61].

However, the relationship between increased cortisol and depression is not consistent and is only apparent in about half of depressed patients[259], therefore other factors must be involved. Furthermore, many investigators have failed to replicate the above findings or have found lowered cortisol levels[260]. Similarly, there are mixed findings with regard to cortisol utility as a measure of prospective risk. Two prospective studies, with samples of between 100 and 200 participants, found no association between cortisol levels and depressive symptoms at assessment, but increased morning cortisol was associated with increased risk of a DD within 12 months[261, 262]. These studies have been further corroborated by a recent study on a relatively small sample of 230 older adolescents who were followed up to one year after the cortisol sampling date. However, a cross sectional study with over 400 participants reported a trend towards lowered morning cortisol in those with a current DD and those with a vulnerability to

depression through increased life stress, but these differences were not statistically significant[263].

Overall, the literature suggests that increased cortisol levels may be a useful marker for depression in cancer patients. Jehn and colleagues[140] (2006) found a difference in cortisol levels in patients with comorbid depression and cancer compared to those with cancer and no depression in a sample of just over 100 patients based on mean plasma cortisol levels. Similarly, urinary cortisol levels (15 hour mean levels) have been reported to be predictive of increased distress in cancer patients one month after treatment, after adjusting for baseline distress, but no pre adjusted findings were reported[264]. Hyperactivity of the HPAA can be assessed by measuring CRH, ACTH or cortisol levels and by use of the dexamethasone suppression test (DST) or DST/CRH test. The least invasive method of measuring HPAA overactivity relies on salivary cortisol levels. Measuring the morning rise cortisol level is a useful and reliable tool for assessing HPAA activity[265].

8.1.3 Inflammation and depression

Evidence of the effects of cytokines on mood has been found through three types of studies: cytokine therapy studies, differences in levels of inflammation in depressed and non-depressed individuals, and neurobiological in vivo and in vitro studies investigating potential mechanisms by which cytokines may induce a change in mood.

IL6, interleukin-2 (IL2) and interferon-alpha (IFNα) (no studies report findings from IFNγ) have been shown to induce low mood and sickness behaviour in patients and monkeys undergoing cytokine therapy[91, 92, 266, 267]. Also, one study showed that small increases in inflammatory mediators caused by an injection of the Salmonella typhi vaccine correlated with a decrease in mood, even though no febrile symptoms were reported[268]. However, Pasquini *et al*.[269] found differences

in symptoms between those who had cytokine induced depression and MDD unrelated to cytokine elevation. They found that feelings of failure, guilt, dissatisfaction and self-dislike were all higher in MDD patients compared to those with IFNα induced low mood. The mood altering effects of inflammation are especially relevant in studies involving cancer patients, due to the cancer related increase in levels of inflammation.

Studies comparing actively depressed patients and controls have found increased levels of cytokines and CRP in patients with a DD[85, 252, 270-273]. Two recent meta-analyses have reported significantly higher levels of IL6 in depressed patients[87, 90]. One meta-analysis found CRP and IL6 to be significantly positively associated with depression, with respect to those with a DD and when assessed by self report measures. This meta-analysis also found significantly increased levels of IL1 in depression, but only when adjusting for BMI and not differentiating between IL1ß and IL1α[87]. A more recent and comprehensive set of meta-analyses[90] only included studies which used DSM criteria and assessed TNFα, interleukins 1ß, 2, 4, 6, 8 and 10 and IFNγ. The conclusion was that only TNFα and IL6 were significantly higher in depressed patients. Only one out of four studies found IFNγ to be significantly higher in those with MDD compared to controls[271]. Although some large studies (over 200 participants) still report no differences (e.g. Steptoe *et al.,* 2003[274]) this may be due to choice of questionnaires, covariates or non specific timing of blood sampling, which is crucial given the circadian rhythm of cytokine production. However, the same group also reported CRP and IL6 to be inversely associated with positive affect in women (only) in a much larger sample of almost 3000 participants[252].

Many studies have also reported decreases in IL-6 or TNFα levels following anti-depressant treatment[258, 275-278] further supporting the correlation data and suggesting a state, rather than trait, relationship between depression and inflammation. This is supported by another study showing that IL6 was not related to trait levels of depressive symptoms but was related to state depressive

symptoms, over a 20 week study period[279]. Moreover, they found that changes in trait scores had an even greater association with IL6. However, one longitudinal study found that high levels of inflammation (IL6 and CRP) were associated with increased cognitive symptoms of depression 12 years after the sampling date[280]. These findings, together with the cytokine induction studies, suggest that cytokines may have a role in the development of depression.

Of particular relevance to this study is that, as stated above and in chapter 1, inflammation is also increased in cancer patients and IL6 has been shown to increase in response to both physical and psychological stress[94, 95]. Notably, levels of inflammation increase after surgery[281]. That, and the findings that cytokines have induced low mood, suggest that inflammation may be a useful marker for risk for depression in cancer patients. Three out of four studies found increased levels of IL6 in cancer patients with a current DE compared to cancer patients without a DD[138-140]. One study found lower post surgery increases in IL6 in those with a current DE at the time of surgery compared to those without[137]. However, the same study found increased levels of IL6 in those with high depressive symptoms. Two of the studies that found an association between increased IL6 and a comorbid DE were carried out on cancer patients either planned for or undergoing chemotherapy[138, 140] and the other study does not report the cancer status[139]. Thus, it is possible that those with a DD have a decreased inflammatory response to surgery, though other studies have shown an increased inflammatory response in those with vulnerable depression (through PH or CT) to either physical or social stress[117, 282]. Also, this study reports contradictory findings of a positive association between depressive symptoms and IL6 suggesting that the results may be unreliable. There have also been reports of an association between increased inflammation and poorer QoL in CR cancer patients[98]. Overall, the literature suggests that higher levels of inflammation would be expected to increase the risk of a DE6 in CR and HN cancer patients.

Levels of inflammation in cancer patients can be measured by many methods; peripheral levels, stimulated monocyte production, tumour expression or cellular genetic transcripts. To make matters more complicated, peripheral levels do not always correlate with that of the normal tissue or tumour expression of markers[234]. Miki and colleagues[234] (2004) found increased circulatory CRP to be associated with increased tumour IL6 expression, but not IL6 expression in healthy mucosa and there was no association between CRP and TNFα. The easiest and therefore most clinically useful method of assessing cytokines is to measure peripheral levels in blood. Cytokine levels are expected to increase after surgery and then return to baseline[197]. Past studies suggest many cytokines may be potentially useful as risk markers but that IL6, TNFα, IL1ß and IFNγ and CRP are the most promising. Therefore, in this study it was expected that IL6, TNFα, IL1ß, CRP and possibly IFNγ would be associated with increased risk of a DE6 in cancer patients. Higher levels of inflammation were also expected to be associated with increased depressive symptoms and poorer QoL.

8.1.4 Conclusions

In summary, both dysregulated stress hormone levels and higher levels of inflammation have been found to be associated with depression. Cancer patients with depression are also reported to have increased levels of IL6. Raised inflammation is of particular importance in cancer patients because tumours express cytokines leading to increased peripheral inflammation, therefore those at risk of depression may be more susceptible to an episode after a cancer diagnosis. Also cytokines are proposed as mediators of tumour progression and markers of poor prognosis. Both dysregulated cortisol and increased inflammation are potential risk markers for development of a DE soon after a cancer diagnosis.

8.2 Results

The results are presented following a similar structure to the previous results chapter on psychological variables except that inflammation was measured at

multiple time points. The results are shown first for cortisol and then for each of the cytokines, structured by time and diagnosis, starting with CR patients at baseline. Two regression techniques are used in the analyses (using robust and bootstrap standard errors respectively) to increase the validity of the findings, as detailed in section 5.4. The results of the regressions with robust standard errors are reported in the prose, but only the bootstrapped parameters are presented. The confidence interval parameters when using robust standard errors are reported in appendices, as referenced below.

8.2.1 Cortisol

8.2.1.1 Descriptives

As can be seen in figure 8.1 the cortisol levels conform to the expected pattern of high waking levels, followed by a further sharp increase and then decreasing to relatively low levels by the evening. There were no significant differences between CR and HN patients. Full descriptives of the cortisol levels are provided in appendix 8. 1.

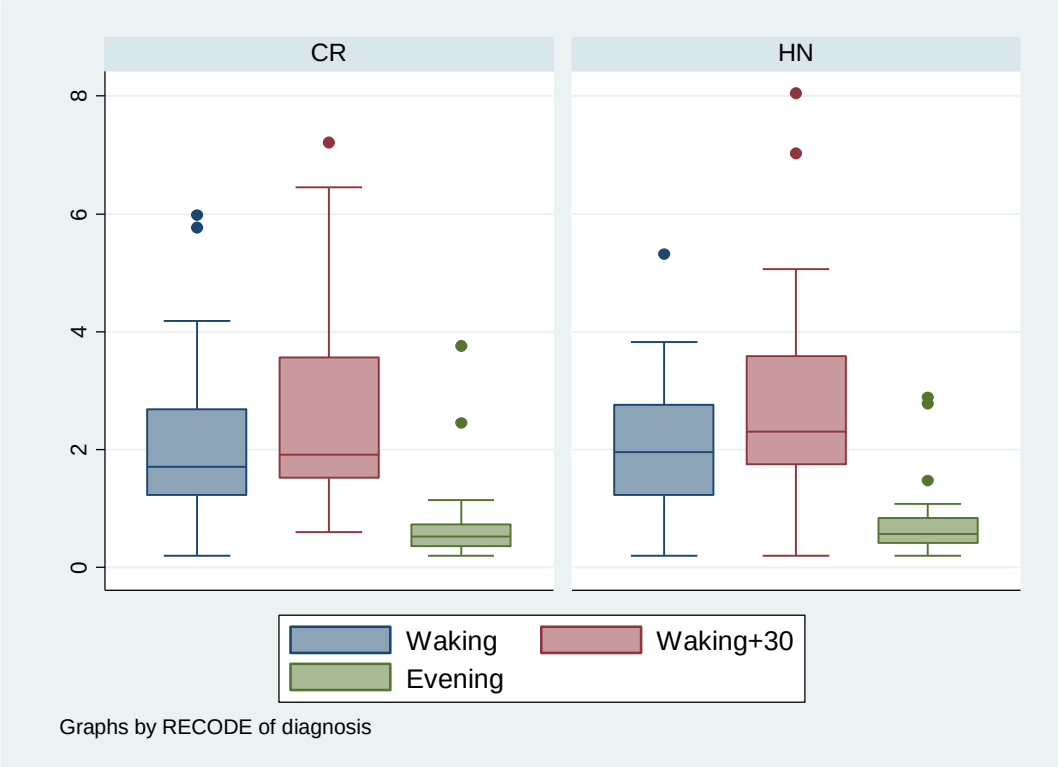


Figure 8.1: Mean cortisol levels by diagnosis.

8.2.1.2 Depression findings

There were no significant associations between cortisol and depressive symptoms at T1, T3 or T4, in either patient group. There was a negative association between depressive symptoms at T5 and cortisol morning rise in CR patients *[N=19, ß(CI)=-0.83 (-1.49 to -0.16) p=0.018]*. However, this association was not significant when using bootstrapped standard errors *[ß(CI)=-0.83 (-1.76 to 0.10) p=0.082]*. There were no significant findings in the HN group.

There were no significant findings between cortisol and depressive symptoms overall, or over time, using longitudinal analyses. Similarly there were no significant associations between cortisol levels and risk of a DE.

8.2.1.3 Quality of life findings

There was no interpretable overall pattern of associations between cortisol and QoL. All of the parameters for the cortisol regressions using robust standard errors are provided in appendix 8. 2. However, there were some isolated findings, which are reported below.

There was a significant association between an increased morning rise in cortisol levels and T1 QoL in CR patients which was still significant when using bootstrapping *[ß(CI)=5.80 (0.17 to 11.43) p=0.043]*. There were no significant findings in the HN group.

At T3 there were no significant findings in the CR group. However, in HN patients, there was a significant negative association between higher evening cortisol and reduced QoL, which remained significant when using bootstrapping techniques *[ß(CI)=-16.65 (-31.23 to -2.06) p=0.025]*.

At T4 there was a significant positive association between Qol and cortisol levels at waking+30 and increased morning rise cortisol in CR patients. After bootstrapping, the association between 30 minute waking cortisol and increased QoL remained *[ß(CI)=5.01 (0.40 to 9.62) p=0.033]* but the association between morning rise cortisol and QoL was reduced to a trend *[ß(CI)=5.16 (-0.48 to 10.79) p=0.073]*. There were no significant findings in the HN group.

At T5 there was a significant positive association between morning rise cortisol and global QoL in CR patients, which was still significant when using bootstrapping *[ß(CI)=6.64 (0.68 to 12.59) p=0.029]*. There was also a significant negative association between evening cortisol and QoL in HN patients. As with the CR finding this was still significant when using bootstrapping *[ß(CI)=-15.83 (-29.48 to -2.17) p=0.023]*.

Overall, there was a significant association between increased cortisol morning rise and increased QoL in CR patients, but this finding was reduced to a trend after calculating bootstrapped standard errors *[ß(CI)=4.93 (-0.34 to 10.20) p=0.067]*. There were no significant findings using longitudinal analyses in the HN group.

8.2.1.4 Summary

The findings did not support the hypothesis that increased cortisol levels and increased cortisol morning rise are associated with increased depressive symptoms and therefore decreased QoL. On the contrary, there is some evidence that an increased cortisol morning rise was associated with increased QoL in CR patients.

8.2.2 Inflammation

8.2.2.1 Descriptives

Figure 8.2 to figure 8.5, summarise the descriptives for all the inflammatory markers used in the study. Levels of T2 IL6, T1 and T2 TNFα and T2 CRP were all significantly higher in the CR cancer patients, compared to the HN patients. However, T3 IFNγ was significantly higher in the HN cancer patients. Full details are provided in appendix 8. 3. As can be seen by the graphs, IL6 and CRP follow the anticipated pattern of an increase after treatment followed by a decline to near baseline levels at one month (see section 8.1.3). However, whilst TNFα follows the same expected pattern in CR groups, it gradually increases in the HN group. Similarly, IFNγ levels show no significant change in CR patients but continue to increase in HN patients. More details are provided in appendix 8. 4.

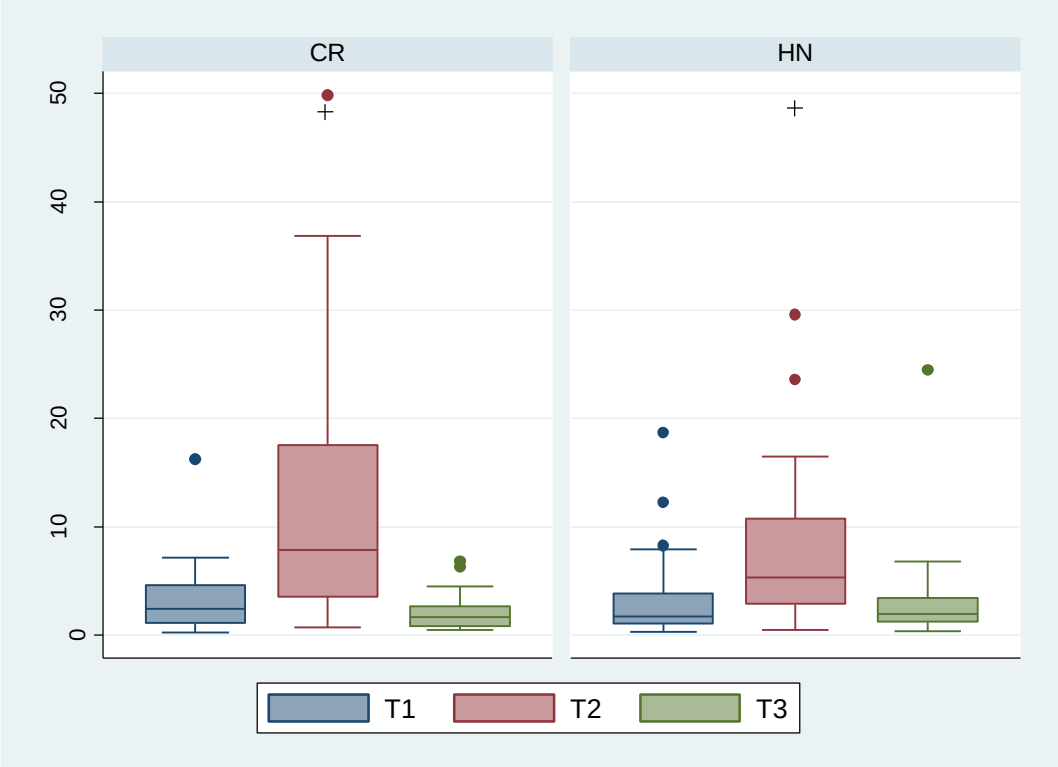


Figure 8.2: IL6 levels at each time point by diagnosis. +significantly higher than baseline levels p<0.05. Two CR patients levels were not included in this graph; their levels were 124.61 and 123.96.

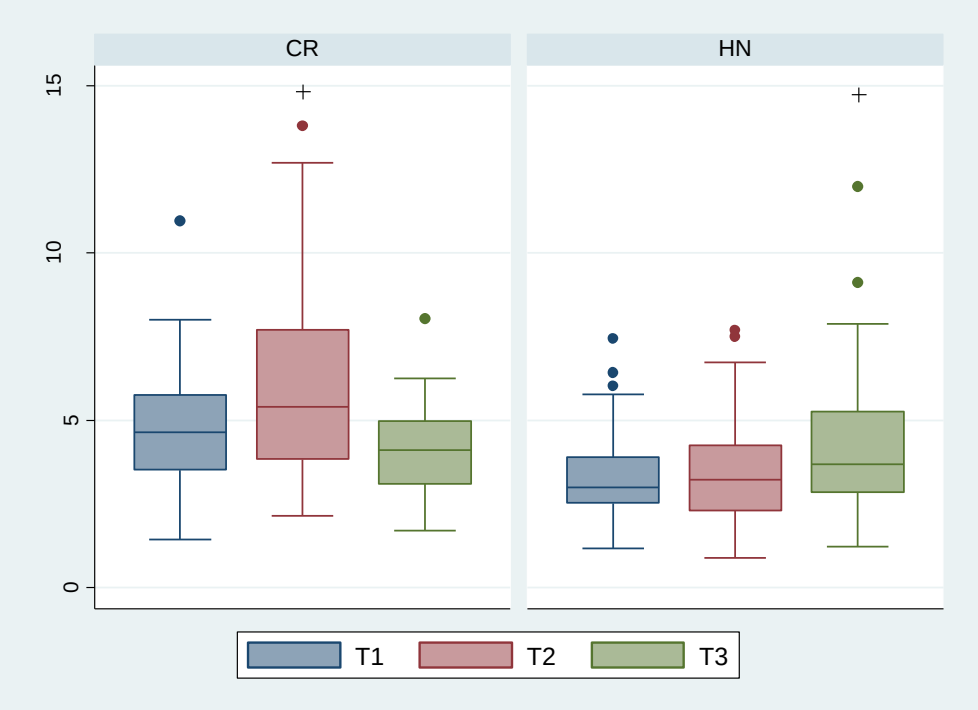


Figure 8.3: TNFα levels at each time point by diagnosis. +significantly higher than baseline levels p<0.05.

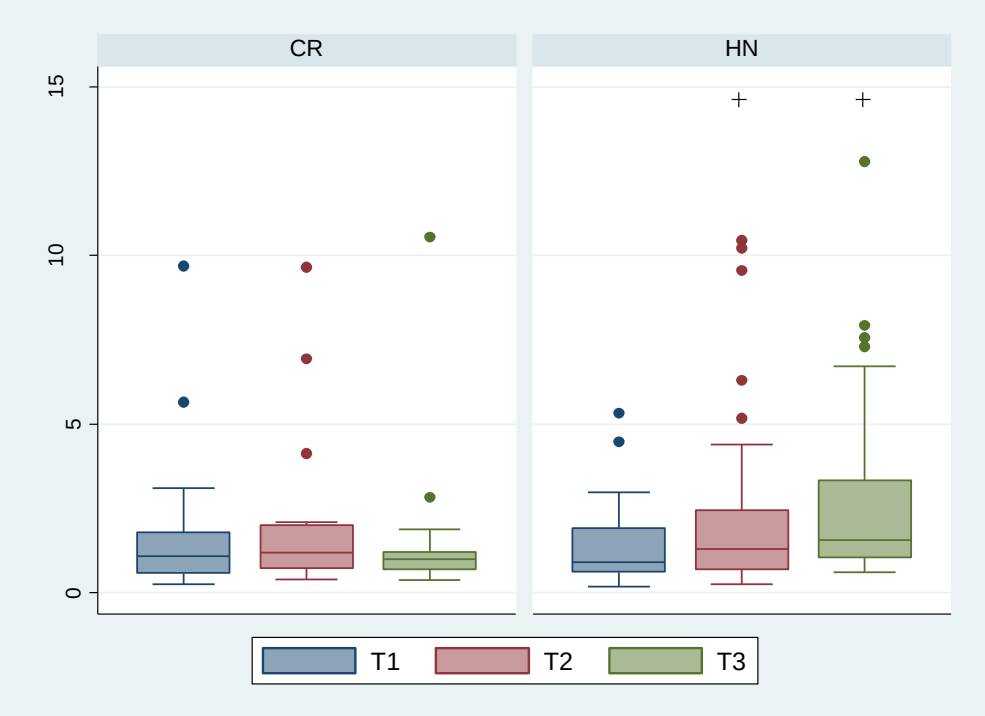


Figure 8.4: IFNγ levels at each time point by diagnosis. + significantly higher than baseline levels p<0.05. Levels from two CR patients were excluded from this graph (135.80, 54.85) and one HN patient (30.26).

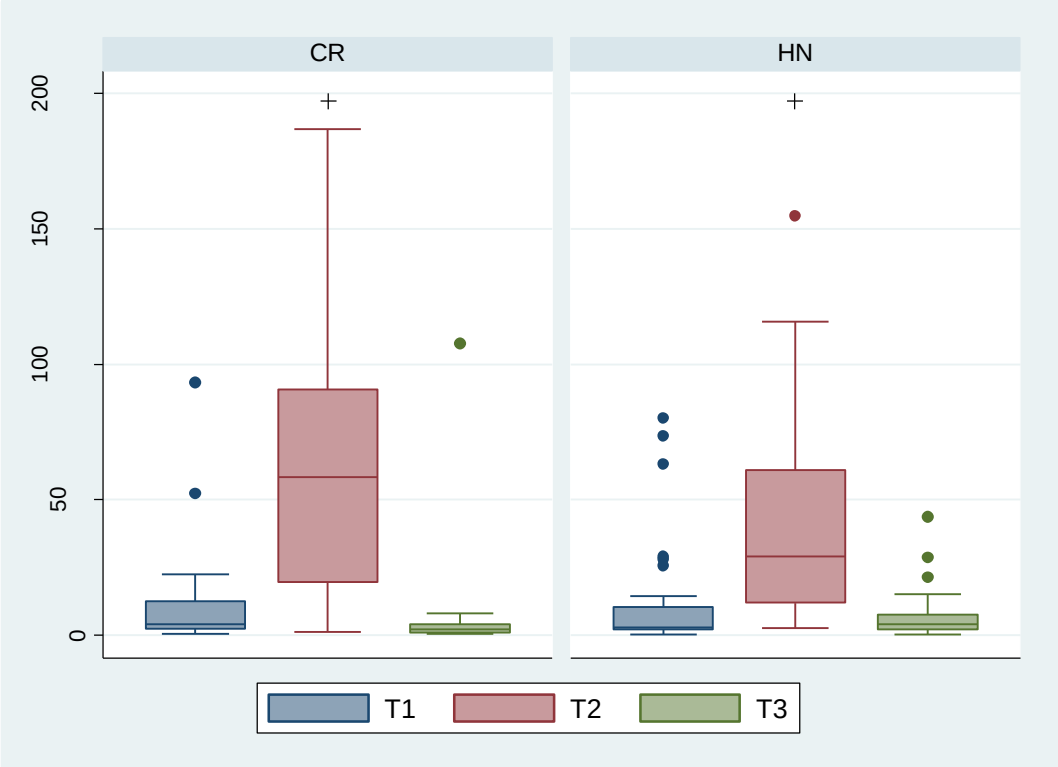


Figure 8.5: CRP levels at each time point by diagnosis. + significantly higher than baseline levels p<0.05. Levels from four CR patients were excluded from this graph (319.45, 213.8, 224.4, and 205.17) and one HN patient (243.42).

8.2.2.2 Depression findings

Consistent with the cortisol results, only the regression parameters for the bootstrapped standard errors are reported here; the parameters for the regressions using robust standard errors are all reported in appendix 8. 5 to appendix 8. 16.

Depressive symptoms at T1:

There was no evidence to suggest an association between increased inflammation at T1 and depressive symptoms at T1 in either cancer group.

Depressive symptoms at T3:

At T3 there was a positive association between T1 IL6, TNFα, IFNγ and CRP and HADS-D in CR patients, but only the TNFα association remained significant after

bootstrapping *[N=20, p=0.190;N=21, ß(CI)=0.95 (0.25 to 1.66) p=0.008; N=21, p=0.570; N=21, p=0.280]*.

At T3 there was also a positive association between T2 and T3 IFNγ and HADS-D in CR patients, but neither of these were significant after using bootstrapped standard errors *[N=23, p=0.523; N=21,p=0.550 respectively]*. Similarly, evidence was found in support of an association between increased perioperative IFNγ and increased HADS-D. Again, this was no longer significant when using bootstrapped standard errors *[N=21, p=0.419]*.

There were no significant associations between T1 or T2 inflammation and T3 HADS-D in CR patients, but there was a significant association between T3 IL6, TNFα and CRP and HADS-D at T3 in HN patients. Only the TNFα finding remained significant after bootstrapping *[N=33, p=0.177;N=33, ß(CI)=0.78 (0.07 to 1.48) p=0.030; N=33, p=0.634, respectively]*.

Depressive symptoms at T4:

At T4 there was a positive association between T1 IL6, TNFα, IFNγ and CRP and HADS-D in CR patients. As with depressive symptoms at T3, only the association between T1 TNFα and HADS-D remained when using bootstrapping *[N=20, p=0.124; N=21, ß(CI)=1.04 (0.09 to 2.01) p=0.033; N=21, p=0.342; N=21, p=0.236, respectively]*.

In CR patients there was a positive association between T2 IFNγ and HADS-D at T4. There was also a significant association between T2 TNFα and HADS-D. Again, only the TNFα finding remained significant when using bootstrapping *[N=23, p=0.617; ß(CI)=1.02 (0.15 to 1.90) p=0.022 for IFNγ and TNFα respectively]*. There were no significant associations between T3 inflammation and HADS-D at T4 in CR patients, but there was a trend towards an association between T3 TNFα and HADS-D. This trend was slightly reduced when using bootstrapped standard errors *[N=22, ß(CI)=1.09 (-0.14 to 2.32), p=0.082]*. Finally, as with T3, evidence was

found in support of an association between greater post operative rise in IFNγ levels and increased HADS-D scores, but this did not remain significant in the bootstrapped model *[p=0.478]*.

There were no associations between inflammation and T4 depressive symptoms in the HN group.

Depressive symptoms at T5:

There were few significant associations between inflammation and depressive symptoms at T5. In CR patients there was a significant negative association between T2 IFNγ and HADS-D at T5. This was no longer significant after bootstrapping *[p=0.203]*. There was also evidence towards a positive association between increased perioperative CRP and HADS-D and an association between decreased perioperative IFNγ and HADS-D. After bootstrapping, the CRP finding was still significant *[N=18, ß(CI)=0.03 (0.00 to 0.05) p=0.042*] whereas the IFNγ finding was not *[p=0.198]*.There were no significant findings in the HN group.

There were many associations between T1 inflammation and mood overall when using longitudinal analyses, but very few of these associations were still significant when using bootstrapped standard errors. When using robust standard errors there was evidence towards the following in CR patients:

1. A positive relationship between TNFα at T1 and HADS-D overall, which remained after adjusting for time, but no interaction.
2. A positive association between IFNγ at T1 and HADS-D overall. This disappeared when including the interaction term meaning the association was only significant at T3 *[p<0.0005],* T4 *[p=0.004]* and T5 *[p=0.025]*. The association at T5 was a negative association.
3. No main effect of IL6 T1 or time, but a positive interaction between IL6 T1 and HADS-D levels at T3 *[p=0.035]* and trend T4 *[p=0.079]*.

4. No main effect of CRP, but a significant positive interaction at T3 *[p=0.004]*, yet non significant at T4 *[p=0.145]* and negative at T5 *[p=0.044]*.

There were no significant results in the HN group.

As with the findings using linear regression, only the TNFα finding in CR patients remained significant when using bootstrapped standard errors *[N=28, β(CI)=0.80 (0.30 to 1.31) p=0.002]* and no findings in the HN group were significant.

There were no significant associations between increased inflammation at any time point and increased risk of a DE6, except an association between T3 IFNγ and reduced risk of a DE6 in HN patients, which was no longer significant when using bootstrapped standard errors *[N=34,p=0.340]*.

8.2.2.3 Quality of life findings

QoL at T1:

At baseline, poorer QoL was associated with increased levels of TNFα and a trend towards increased CRP in CR patients. Both the associations between TNFα and CRP and poorer QoL remained significant after bootstrap analyses *[ß(CI)=-5.66 (-11.20 to -0.12) p=0.045; ß(CI)=-0.29 (-0.88 to 0.30) p=0.025 respectively]*. There were no significant findings in HN patients.

QoL at T3:

There were no significant associations in CR patients between inflammation at T1 or T2 and poorer QoL at T3, but there was evidence towards increased T3 IL6, TNFα and IFNγ and poorer QoL at T3 in CR patients.

The only association that remained significant when using bootstrap analyses was with TNFα and QoL *[N=20, p=0.086; N=21, ß(CI)=-9.10 (-17.47 to -0.72), p=0.033; N=21, p=0.534 for IL6, TNFα and IFNγ respectively]*.

There was a significant association between T2 IL6 and CRP and poorer QoL at T3 in HN patients. Both of these findings remained significant when using bootstrapped standard errors *[ß(CI)=-1.47 (-2.80 to -0.14) p=0.030; ß(CI)=-0.19 (-0.35 to -0.02) p=0.025 for IL6 and CRP respectively]*.

There was also a significant association between increased T3 IL6, TNFα and CRP and poorer QoL at T3 in HN patients. However, the only association that remained significant in the bootstrap analyses was between TNFα and QoL *[N=33, p=0.068; N=33, ß(CI)=-5.37 (-9.97 to -0.76) p=0.022; N=33, p=0.162, for IL6, TNFα and CRP respectively]*.

Higher perioperative IL6 and CRP increase was associated with poorer QoL at T3 in HN patients. These results remained significant using bootstrap standard errors *[ß(CI)=-1.72 (-3.24 to -0.19) p=0.028; ß(CI)=-0.22 (-0.41 to -0.03) p=0.026 for IL6 and CRP respectively]*.

QoL at T4:

At T4, there was a significant association between T2 IFNγ and poorer QoL in CR patients, but this was no longer significant when using bootstrapping *[N=23,p=0.821]*. There was also an association between higher perioperative IFNγ and poorer QoL at T4 in CR. Again, this was no longer significant when using bootstrapping *[N=21,p=0.581]*. There were no significant associations in HN patients.

QoL at T5:

There were no significant associations between inflammation at T1 or T2 and poorer QoL at T5 in CR patients. There was weak evidence towards an

association between increased IFNγ at T3 and poorer QoL in CR patients. However, this association was no longer significant after bootstrapping *[N=19, p=0.632]*. There were no perioperative associations.

In HN patients there was a significant association between T1 IFNγ and poorer QoL at T5 in HN patients. There was also a trend towards an association between increased T1 IL6 and reduced QoL in HN patients. The association between IFNγ and poorer QoL was also significant when using bootstrapping, but the association between IL6 and QoL was not *[N=36, ß(CI)=-4.04 (-7.71 to -0.37) p=0.031; N=36, p=0.228 for IFNγ and IL6 respectively]*. There was also a significant association between increased IL6 at T2 and poorer QoL at T5 in HN patients, which remained significant after bootstrapping *[ß(CI)=-1.21 (-2.29 to -0.12) p=0.030]*. Finally, there was a significant association between increased IL6 at T3 and reduced QoL at T5 in HN patients, which was still significant when using bootstrapped standard errors *[N=32, ß(CI)=-3.73 (-7.06 to -0.41) p=0.028]*. As with the CR patients there were no perioperative associations.

QoL overall:

There was a significant association between T1 IFNγ and CRP and reduced QoL overall in CR patients in longitudinal analyses. These associations were no longer significant when using bootstrapped standard errors *[N=28,p=0.385; N=28,p=0.134 for IFNγ and CRP respectively]*. There were no significant associations in HN patients and no time interactions in either patient group.

8.2.2.4 Summary

There were no consistent findings that could be considered reliable between cortisol and either depressive symptoms, QoL or risk of a DE.

There were consistent associations between increased TNFα and increased depressive symptoms and poorer QoL. These findings were much more robust in the CR group:

- TNFα at baseline was associated with increased poorer QoL at baseline and depressive symptoms at one and three months post surgery.
- TNFα at one week post surgery was associated with increased depressive symptoms at three months.
- TNFα at one month post surgery was associated with increased depressive symptoms at one month.
- There was a trend towards an association between TNFα at three months and poorer QoL at three months – which was also found in the HN group.

The most consistent finding for the HN group was an association between increased perioperative IL6 and CRP and poorer QoL at one month post surgery. Also, increased baseline IFNγ and IL6 at one week post surgery were both associated with poorer QoL at six months.

8.3 Discussion

8.3.1 Cortisol

Counter to the hypothesis, there were no consistent findings that could be considered reliable between cortisol and either depressive symptoms, QoL or risk of a DE.

Overall, cortisol levels followed the expected pattern of higher morning levels, including a 30 minute post waking peak, followed by an evening nadir. However, there were very few significant findings relating cortisol and depressive symptoms, risk of a DE6 or poorer QoL. Although there were some significant associations in the cortisol analyses, there was no discernable pattern, suggesting that the results may not be reliable and would require replication. This may be due to low power

as previous prospective designs all had larger sample sizes[252, 262, 283]. Cortisol levels can be affected by numerous other variables such as smoking, age, LE, time of waking, but this study did not have the power to adjust for all the measured factors without risking over adjustment. Also, although patients reported the time of the first sample, which was not associated with cortisol levels (data not shown) patients did not report the time of waking, thus unreliable reporting and/or varied waking time may have made an impact on the results. Investigations into participant compliance with the sampling procedure found that even though most participants reported full compliance 26% took samples outside of the sampling window[284]. A further study by the same group found that the non compliant samples resulted in flatter slopes[285]. In a recent meta-analysis[260] of over 21 studies, there was a positive association between increased morning rise and life stress, but no association between depression and morning rise. Also, studies investigating morning rise over three days tended to show increased levels, whereas studies using data from two or less sampling days tended to find an inverse association, thus issues of non-compliance may have further confounded the results. One past study[283] found mean urinary cortisol significantly predicted high depressive symptoms after knee replacement surgery, implying that there is a relationship. But a larger sample, and perhaps a more robust protocol, is required to detect a significant effect. It is also possible that inclusion of the DST/CRH test may give more robust findings as it is reported to be more sensitive and 80% of patients test positive[61], but this is much more invasive and demanding of patients.

8.3.2 Inflammation

Increased inflammation was not associated with an increased risk of a DE6, but there were some positive associations between inflammation and depressive symptoms.

Almost all of the levels of inflammatory markers were within detection range, with the exception of IL1ß, which was excluded from further analyses. However, there

was substantial variation between individuals and over time. Most levels increased soon after surgery and then fell back to near baseline by one month after surgery, except TNFα and IFNγ levels which continued to rise in HN patients. Stratifying by radiotherapy indicated that the continued rise was only apparent in radiotherapy patients, which is consistent with previous research[286]. IL6 and CRP also increased at one month post operation in radiotherapy patients, but unlike TNFα and IFNγ, IL6 and CRP were also increased at baseline in those patients that received radiotherapy.

The lack of an association between increased inflammation and increased risk of a DE6 in either patient group could be because of low power. There were many significant findings between inflammation and increased depressive symptoms or poorer QoL in both cancer patients when using standard regression techniques. However, whilst most of these were in the hypothesised direction, some of the relationships were very strong but in the opposite direction. Further investigations revealed that these results were over influenced by outliers. A more conservative approach was used to verify the significant results, which allowed for non parametric distributions and weakened the role of outliers. After using this technique fewer associations were significant, but all were in the hypothesised direction and the findings appeared more reliable. The relationship between inflammation and depressive symptoms and QoL differed between the two cancer groups. There appeared to be a strong relationship between TNFα and increased depressive symptoms in the CR patients, whereas in HN patients the main findings were between IL6 and QoL.

In CR patients, increased TNFα levels were a significant risk factor for increased depressive symptoms for one and three months post surgery. Pre treatment TNFα levels were associated with increased depressive symptoms at one and three months post surgery. Increased TNFα one week after surgery was also associated with increased depressive symptoms three months post operation. Increased TNFα levels at one month post operation were associated with concurrent low

mood and poorer QoL. There was also a trend towards an association between increased TNFα levels at one month post surgery and increased depressive symptoms at three and six months after surgery. Finally, a high perioperative increase in CRP levels was associated with increased depressive symptoms at T5 in CR patients. Interestingly, baseline TNFα and CRP were both associated with poorer baseline QoL in CR patients. As a result, all of the findings were rechecked after adjusting for baseline QoL. It was found that baseline QoL mediated the association between TNFα and later depressive symptoms, but was not as predictive of increased depressive symptoms as TNFα. It is surprising that there were no findings relating to IL6 in this study as IL6 is often reported to be associated with increased depressive symptoms, but the meta-analyses[90] showed a greater effect size for TNFα than IL6, so it is possible that the sample size was only large enough to detect an effect of TNFα, but not IL6.

In HN patients, the only association between inflammation and depressive symptoms was a cross sectional association at one month post surgery between TNFα and increased depressive symptoms. TNFα was also associated with poorer QoL at this time point. There were, however, some prospective findings relating to increased IL6 and poorer QoL. Higher perioperative IL6 and CRP and one week post operative IL6 and CRP levels were associated with poorer QoL at T3. Higher baseline IFNγ, increased IL6 levels at one week post surgery and at one month post surgery were all associated with poorer QoL at six months post surgery. These findings were mediated by the surgical rating score, but were still the strongest predictor of poor QoL at T3 or T5. This relationship is probably due to levels of sickness behaviour, some aspects of which are explored in the next chapter. However, there is not even a trend towards an association between IL6 or CRP and poorer QoL at T4, which is hard to explain given the findings at T3 and T5. There is also less of a relationship between depressive symptoms and QoL at this time point. The reasons for this are not clear, but it may indicate that T4 is a bad time for sampling.

The findings of an association between inflammation and increased depressive symptoms in CR patients do follow a similar pattern to that of the psychological variables, indicated by an increased association at T4 which is much weaker at T5. In HN patients, however, the findings relating to QoL follow the opposite pattern, where no association is apparent at T4, but there are associations at T3 and T5. These findings further confound the strong effects of psychological factors at T4, especially with regard to that of CT, which is associated with depressive symptoms at T4 in CR patients, but not HN patients. This is unlikely given the larger HN sample size. However, they also show that physiological factors can be used as markers for high levels of depressive symptoms or poorer QoL at later time points after surgery. The clinical value of these measures is discussed in chapter 12.

The results suggest that TNFα may be a risk factor for increased depressive symptoms in CR patients, but only within a tight time window. Although there was a trend towards an association between T3 TNFα and later depressive symptoms, these associations were not significant, suggesting that either the increased time difference between the two measures weakened the effect, or possibly that the association between TNFα and depressive symptoms was only apparent soon after surgery and could be a reflection of sickness behaviour[287]. It is interesting that the relationship between inflammation and mood was much less apparent in the HN patients, despite a larger sample. This is most likely due to a combination of two reasons: 1) the CR group is much more homogenous (in terms of cancer site, symptoms, impact of treatment and life style), so any effect within the HN group may have been obscured by covariates such as smoking, cancer site and histology, and treatments 2) inflammation has been proposed as an aetiological factor in CR cancer[229] which may have augmented any inflammatory effects, (e.g. increased inflammation over a longer period, both pre and post operatively). It is also possible that the relationship between inflammation and mood in the HN patients was not as apparent due to lower cytokine levels overall in the HN group, therefore less sensitivity. Most studies that found differences in cytokine levels in

cancer patients with depression, compared to those without, used heterogeneous groups, usually mainly breast or CR cancer patients[137-140].

8.3.3 Limitations and conclusions

This study was limited by low power, especially given the number of variables that may affect the results. The CR and HN patients were analysed separately as previous analyses suggested that they are very different, and accordingly the results differ greatly between the two diagnoses. As is expected in small samples, the analyses were initially greatly skewed by patients with extreme cytokine levels, so two different methods were used and the results were only accepted if both analyses indicated a significant effect. This helped to enhance the reliability of the findings, but did not help prevent a type II error. The original findings are reported because it is noteworthy that the majority of the outliers generated findings in the hypothesised direction, suggesting that an increase in patient numbers and therefore greater data spread is likely to yield more positive results. Even so, some significant effects were found, further indicating that this research area would benefit from using larger more homogenous samples. It was surprising to see no effect from IL6, but such a robust effect between TNFα and depressive symptoms in CR patients, suggesting that it is worth investigating other cytokines. A review of potential biological markers for depression proposed IL10 as one of the most promising cytokines for use as a marker (although no cytokine has a high enough predictive value to be considered for use as yet)[89] so future studies could consider using interleukin-10 (IL10). IL10 has also been found to be a stronger indicator of cancer prognosis in colon cancer patients, over that of IL6[288]. If IL10 levels did not drop after treatment it was indicative of a future recurrence[288]. As IL10 is an anti-inflammatory cytokine the ratio between pro-inflammatory cytokines and IL10 may also be of interest. One study found that the ratio of IL6 to IL10 was significantly higher in depressed patients[289]. Given the low detection level of IL1ß it is probably worth testing IL10 instead of IL1ß.

8.3.4 Summary

In summary, this chapter reported on the value of physiological markers as predictors of depression or poorer QoL in CR and HN cancer patients after surgery. This study found no evidence to support the hypothesis that increased salivary cortisol levels would be associated with increased depressive symptoms; there were no reliable findings between cortisol and later depression or poorer QoL. There was some evidence to support the hypothesis that increased inflammation would be associated with increased depressive symptoms: high levels of TNFα increased the risk of high depressive symptoms in CR patients. Inflammation was only useful as a marker of later depressive symptoms in CR patients. However, IL6 and CRP were a marker of poorer QoL in post surgery HN patients. Due to low power and some unexpected findings it is hard to make firm conclusions, but these results suggest that inflammation shows promise as a marker for post surgical mood and QoL in the two cancer groups and is therefore worthy of more investigation. Inflammation may also be related to many other aetiological aspects of depression and cancer symptoms; the next chapter further investigates the inter-relationships between the psychological and physiological markers included in this study, which have been investigated in this and the previous chapter.

9 Covariates

The last two chapters have focused on the relationships between psychological and physiological factors and depression and QoL. However, as reported in the literature review and the hypotheses diagram (see page 58) it is likely that many of the investigated psychological and physiological variables are inter-related. Therefore, this chapter addresses part of the third aim of the thesis: to explore associations between other possible explanatory factors on inflammation and cortisol. It will also test the fifth hypothesis: that patients with increased HPAA activity will show increased inflammation. This chapter demonstrates the inter-relation between the investigated variables, by reporting associations between:

1. Psychosocial variables involved in the aetiology of DDs (CT, NE, LE).
2. Physiological variables (cortisol and inflammatory markers).
3. Physiological variables and psychosocial variables.
4. Psychosocial variables and symptoms of fatigue and pain.

This will introduce the rationale behind the choices of covariates in the final adjusted models presented in Chapter 10.

9.1 Background

9.1.1 Psychological variables

Many of the variables under investigation are likely to be related. Past studies have demonstrated relationships between many of the investigated factors, and many of the aetiological factors that occur earlier in life are expected to be associated with a PH depression; depression is a recurrent disorder with an average age of onset of 25 years[199] whereas CR or HN cancers are more likely to occur in patients over the age of 50. Therefore, most cancer patients with a vulnerability to a DD, such as high levels of NE, are likely to have already experienced a DE.

9.1.1.1 Childhood trauma

There is evidence that CT is related to NE, LE and PH depression. Kendler's model[62] of risk for development of a DE (introduced in sections 1.2.2 and 7.1), reported an association between disturbed family environment and childhood sexual abuse and NE. Similarly a more recent replication of Kendler's model by Sjöholm's group[200] found disturbed family environment increased the risk of NE, but found no association between parental loss and NE. This suggests that the relationship between CT and NE may be dependent on the form of CT experienced. Another retrospective study found a relationship between three or more childhood stressful events (ranging from family discord to traumatising accidents) and NE in over 700 participants all free from mental illness[290]. Finally, one study using the CTQ found an association between emotional abuse and NE in those with a DD[291], but no significant association with any other scale and they did not report the CTQ total score. Thus an association between CT and NE would be expected.

Kendler's group[62] also found sexual abuse to be associated with increased difficulties and independent stressful LE in the past year. They found an

association between disturbed family environment and lifetime trauma, difficulties and marital problems in the last year. Similar results were obtained by Sjöholm's group[200]. As stated in the section 1.3.3 and 7.2.1 CT is also associated with a DD, so those patients with high levels of CT are also more likely to have a PH depression, though interestingly neither Kendler[62] or Sjöholm[200] report a direct association between CT and PH depression, perhaps due to adjustments for confounding factors. Based on these findings CT is hypothesised to be associated with NE, LE and PH depression.

9.1.1.2 Neuroticism, life events and PH depression

In addition both Kendler's[62] and Sjöholm's[200] models found that NE was associated with marital problems but not life difficulties, such as daily hassles, LE or PH depression. The lack of association between NE and LE or PH depression is likely to be due to confounding factors, as previous reports have shown a strong relationship between NE and LE and past mental health[228]. Investigators have also reported that the risk of a DE after a stressful LE is amplified in those with higher levels of NE[228]. Kendler's group[292] replicated these findings with a larger sample of 7,500 (compared to 160). Based on these findings NE is hypothesised to be associated with LE and PH depression.

Finally, both Kendler's[62] and Sjöholm's group[200] found that PH depression was associated with dependent stressful LE (where the person's behaviour may have contributed to the event as rated by an independent informant). It is a well documented finding that individuals with a current DE or in remission from a DE are more likely to generate stressors, particularly those involving interpersonal conflicts[293, 294]. Based on these findings PH depression is expected to be associated with more LE.

9.1.2 Physiological variables

There is now a substantial amount of evidence to suggest a bidirectional link between cortisol and inflammation[295]. Inflammation has been reported to increase HPAA activity[296] and equally, glucocorticoids have been found to potentiate and suppress immune activity[297]. Evidence for this association has been found through correlations in animal and human samples and challenge studies.

Challenge studies have shown a suppressive effect of cortisol on inflammation. High cortisol levels have been associated with lower IL6 responses after a stressor in 199 middle aged participants, suggesting a suppressive effect of glucocorticoids. Cortisol responders also expressed more subjective stress during the tasks[298]. Similarly, pulsatile infusion of cortisol increased cortisol levels and significantly decreased levels of IL6 and TNFα in a small sample of 14 depressed patients[299]. However, the relationship between cortisol and inflammatory activity appears to be dependent on timing; glucocorticoids can potentiate immune activity in response to immune challenge, demonstrated by increased IL1, (but not IL6) but only if the glucocorticoid is administered before the immune challenge. Glucocorticoids were found to have a suppressive effect on cytokines if administered from five minutes after the immune challenge[297].

Challenge studies have also demonstrated that inflammation activates HPAA activity; IL1 administration increased an immobilisation stress associated ACTH rise, as well as dopamine and serotonin levels[300]. All of these effects could be prevented by using an IL1 receptor antagonist, providing the antagonist was administered before immobilisation stress started. Pro-inflammatory cytokines are thought to activate the HPAA by increasing glucocorticoid resistance[80] and thus increasing CRH production. Cytokines also stimulate vasopressin which stimulates ACTH production[296]. Correlation studies[85] have shown a time lagged correlation between IL6 and later cortisol secretion (of about 6 to 7 hours)[85]. Similarly, evening cortisol levels were found to correlate with immune stimulated

mononuclear cell TNFα levels, but not IL6 levels[250]. However, this relationship may be dysregulated in those with depression as those with MD did not show the time lagged association between IL6 and cortisol that was present in healthy controls[85]. Similarly, further work has reported that IFNα induced depressive symptoms are related to cytokine levels, but not to HPAA dysregulation[301]. Interestingly, one study also found that monocytes incubated with dexamethasone (a glucocorticoid receptor agonist) from patients with a DD produced more TNFα compared to those of healthy controls[302], but only in monocytes from those individuals who responded to treatment (with amitriptyline). This suggests that there is a complex relationship between cytokines and the HPAA, which may be dysregulated in some patients with a DD.

Taking all of the studies into account, there clearly appears to be a relationship between inflammation and cortisol, though some of the results are a little conflicting. Differences in these results are likely due to the instability of cytokines, the reliability of testing protocols. It is also possible that there is a dysregulation in the relationship between patients with depression, which may depend on the aetiology or subtype of depression[269, 301, 303, 304]. However, most studies show a correlation between inflammation and cortisol. Therefore it was hypothesised that there would be a positive correlation between cortisol and inflammatory markers.

9.1.3 Childhood trauma, neuroticism, life events, past history of depression and cortisol

For the first nine months of life the HPAA has an irregular secretory pattern, which starts to show a regular rhythm from 12 months[259]. Numerous animal and human studies have shown a relationship between increased CT and increased HPAA activity. Although the picture is complex[255], those with CT appear to show higher cortisol levels then those without. Individuals with ELS also appear to be more responsive to social stress tests[305], although most of these findings use plasma ACTH and not cortisol measures. Increased plasma cortisol response after a

social stressor has been reported in those with depression and high levels of ELS, although there was no difference in those with CT or MDD only and controls[106]. A recent prospective study also found higher salivary cortisol and plasma ACTH in men and women that had been separated from both parents (but not from their fathers only) during early childhood because of world war two. They also found a greater effect if separated from their parents earlier[306]. On the other hand, they only found a difference in stress reactivity in the male sample, where those who were separated from both parents showed greater cortisol increases in response to a social stress test. These findings were based on a sample of 282 older subjects and the associations were only reported after adjusting for current depressive symptoms. Nevertheless, contradictory findings of decreased salivary cortisol awakening in undergraduate students who had experienced early life loss have also been reported[307]. Of note, many studies report HPAA hypoactivity in those suffering from chronic stress, post traumatic stress disorder and chronic fatigue. Hypoactivity of the HPAA is characterised by flattened cortisol awakening response and lower levels of cortisol overall. Childhood trauma also increases the risk of post traumatic stress disorder[308] and chronic fatigue[255] it is possible that the spread of HPAA abnormalities obscures any relationships due to the inclusion of subgroups with diametrically opposed HPAA dysregulation. Thus cortisol levels would be expected to be higher in those who reported higher levels of CT.

A number of studies have also found a relationship between current stress and salivary cortisol levels. Increased cortisol awakening response has been reported in those experiencing chronic stress[253], but the authors did not investigate the prevalence of mental illness within their sample. Of relevance to this study, a greater cortisol response to awakening has also been associated with number of severe LE in the previous month, though less severe LE had no association[263]. However, the authors found lowered morning salivary cortisol in the same sample in those with a current DD, suggesting the sample may not have been representative. Despite a long pathway from psychological stress to increased salivary cortisol levels, the evidence suggests increased levels of salivary cortisol

in those under chronic stress and who have experienced recent severe LE. Thus, cortisol levels would be expected to be higher in those reporting more LE.

Similarly there is evidence to suggest an association between NE and increased HPAA activity. Healthy individuals free from any psychiatric disorder but with high levels of NE have been reported to have significantly higher cortisol levels at 30, 45 and 60 minutes after waking compared to those with low NE scores[115]. Although they did not adjust for current depressive symptoms which appeared to be higher in the highly neurotic group. Increased morning rise has also been shown to be associated with NE in breast cancer patients, but no association was found between NE and cortisol in the control group in that study[309]. However, despite these positive findings a recent meta-analysis reported no association between cortisol awakening response and NE[260].

Two studies have shown a positive association between a PH of depression and increased morning rise[251, 310]. One of those studies included 579 remitted MDD patients with 701 current MDD patients and 308 controls and found higher morning rise cortisol levels in the remitted and current MDD patients compared to controls.

Past research suggests that patients with CT, recent severe LE, a PH of depression or high levels of NE have dysregulated HPAA which would probably result in an increased cortisol awakening response.

9.1.4 Childhood trauma, neuroticism, life events, past history of depression and inflammation

As stated previously, psychological and physical stress increase cytokine levels[94, 95, 116, 300]. There is also a lot of evidence to suggest a relationship between increased inflammation and CT and ongoing stress. Past studies have reported an association between CT and increased inflammation in adulthood. A prospective study involving over 800 participants reported a dose response relationship

between no abuse, probable abuse and definite abuse and CRP levels[311], leading the authors to estimate that ELS could account for 10% of low grade inflammation in adults. These findings are supported by studies showing increased inflammation in animals after ELS (reviewed by Jessop 2009[312]). Also, perhaps of particular relevance to this study, a previous investigation found that social isolation stress increased colonic TNFα levels in rats that were exposed to psychological stress or no stress, but not when rats were subjected to experimentally induced colitis[313]. However, one study reported increased inflammation in response to a stressor in those with MDD, but it did not find a relationship between CT and increased inflammation or increase in inflammation following a social stress test in a sample of 27 volunteers[116]. Indicating that perhaps present depression and current stress have a greater association with inflammatory reactivity then earlier life stressors. Studies have also reported higher increases in levels of IL6 in women with a PH depression soon after childbirth[282]. These studies imply that those at risk of a DD show increased inflammatory responses to stress, suggesting that cancer patients who experienced CT have a PH depression or experience other stressors at the time of diagnosis may show increased inflammation compared to those without these risk factors.

There are fewer reliable studies investigating relationship between NE and inflammation. One study found no relationship between NE and IL6 in a group of 103 participants over 40 years of age. However, two thirds of their samples were taken in the afternoon and the lack of consistency in the sampling time would have affected the results[314]. A smaller study of 44 patients found a positive association between NE and IL6 levels in older adults, based on stimulated monocyte IL6 production from a morning blood sample[118].

Additionally, there is evidence towards an association between depression and prospective increases in inflammatory markers[315]. Hamer and colleagues[315] (2009) found an association between chronically high levels of depressive symptoms and increased CRP levels two years later based on a sample of over

3500 older adults. It is possible that the link between inflammation and depression is bidirectional, thus the relationship between baseline depressive symptoms and later inflammation was investigated. However, the relatively small effect may be confounded by the presence of current psychological and physiological stress experienced by newly diagnosed cancer patients. Studies in physically healthy subjects report a greater increase in IL6 in response to psychological stress in those with a DD compared to those without depression[116]. Whereas, studies in CR cancer patients have reported a decreased IL6 response to surgical cancer treatment in those with a DD[137]. Nonetheless, baseline depressive symptoms were expected to be associated with increased inflammation post treatment.

9.1.5 Psychological and physiological markers of fatigue and pain

Past studies have suggested that pre diagnostic factors have an effect on somatic symptoms. For instance, cancer patients' reports of somatic symptoms on the EORTC-QLQ were reported to be primarily affected by negative affect, or their emotional function score, more so than their overall health status as determined by a physician based on their physical function[148]. Similarly, NE has been associated with not only poorer QoL in HN patients, but also with greater fatigue, pain, dyspnoea, insomnia, diarrhoea and financial difficulties[212]. Negative affect has also been reported to be associated with more pain[316]. Childhood trauma has also been associated with increased physical symptom complaints in primary care patients in a retrospective study[317]. In line with these findings, higher IL6 scores have not only been associated with clinician rated function, but also increased nausea and fatigue[142], which is perhaps not surprising given the well founded relationship between raised inflammation and sickness behaviour, of which pain sensitivity and fatigue are two of the most prominent features[287].

Testing for relationships between all of the proposed risk factors and somatic symptoms would not be practical and could result in many chance findings due to multiple testing. However, the relationship of the risk factors under study to

somatic symptoms is important to help interpret the fully adjusted models which are presented in the next chapter, and also to demonstrate the complexity of relationships between psychological and physiological markers and QoL. Based on the above reports, the relationships between the markers under study and fatigue and pain scores were investigated. Both psychological factors and increased inflammation were expected to increase fatigue and pain reporting.

9.1.6 Conclusions

The investigated psychological and physiological markers are likely to be related to each other. There is strong evidence for an association between increased CT and current stress and increased inflammation, and probably increased HPAA activity. There is also strong evidence towards an association between HPAA activity and inflammation. Finally, there is also evidence to suggest a relationship between all of the risk factors for depression and increased symptom perception. This chapter reports the results for the most salient of these relationships, thereby incorporating the previous two results chapters and introducing the rationale for the final adjusted models presented in chapter 10.

9.2 Results

The results are presented following a similar structure to the literature review. The results are shown first for inter-relationships between psychological variables, then the relationship between cortisol and inflammation, structured by time and diagnosis, starting with CR patients at baseline. This is followed by a section investigating the relationship between psychological variables and levels of cortisol and inflammation, finally, finishing with the relationship between all of the variables and symptoms of fatigue and pain. Consistent with chapter 8 on physiological factors, two regression techniques are used in the physiological analyses (using robust and bootstrap standard errors respectively) to increase the validity of the findings, as detailed in section 5.4. The results of the regressions with robust standard errors are reported in the prose, but only the bootstrapped parameters

are presented. The confidence interval parameters when using robust standard errors are reported in appendix 9. 1 to appendix 9. 3.

9.2.1 Psychological variables

9.2.1.1 Childhood trauma and neuroticism

There was little evidence towards an association between CT and NE in CR patients *[N=19, p=0.222*]. There was weak evidence towards an association in HN cancer patients between CT and NE *[N=34, ß(CI)=0.07 (-0.01 to 0.14) p=0.068]*. Both sets of data were following a similar trend and when the two were combined there was a significant positive association between total CTQ score and EPQ-N *[N=53, ß(CI)=0.08 (0.01 to 0.14), p=0.021]* indicating a weak but significant effect (see figure 9.1).

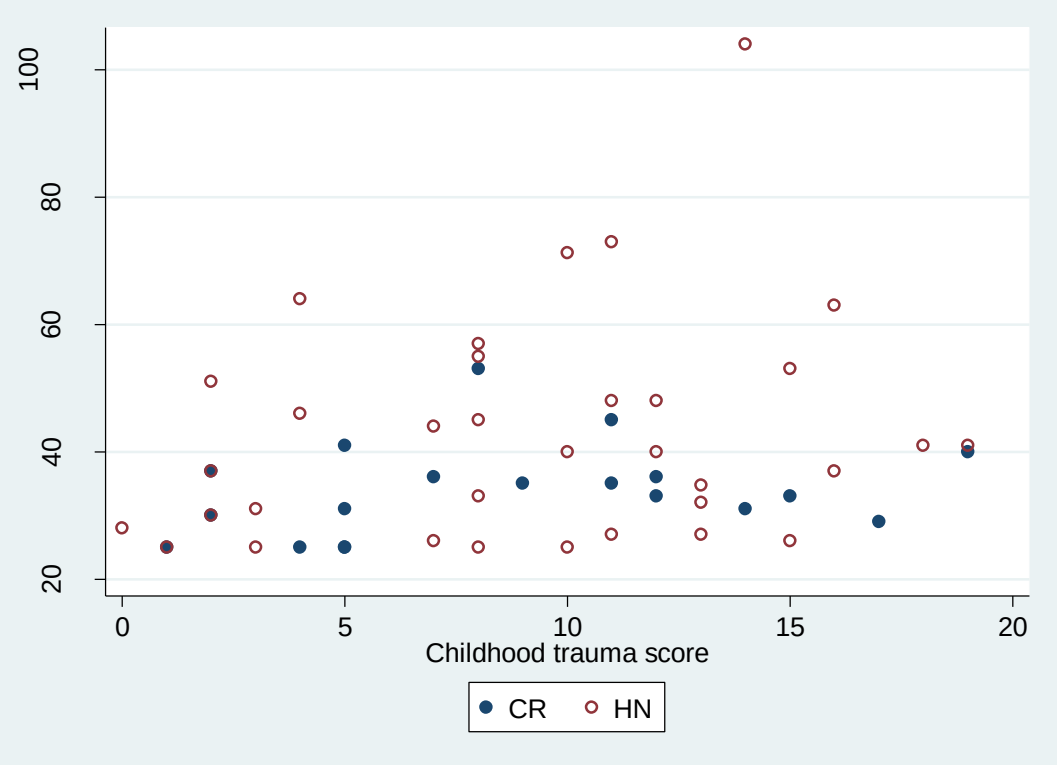


Figure 9.1: Association between CT and NE.

9.2.1.2 Childhood trauma, neuroticism and past history of depression

There was no evidence towards a relationship between CT and PH depression.

As expected high NE was associated with a PH of depression *[N=62, OR(CI)=1.29 (1.10-1.51) p=0.002]*.

9.2.1.3 Childhood trauma, neuroticism, PH depression and life events

Childhood trauma, NE and PH depression were all associated with increased LE reporting. There was a weak trend towards an association between CT and LE in CR patients *[p=0.168]* and a significant association in HN patients, so the results were combined and gave an overall significant effect *[N=52, ß(CI)=0.03 (0.01 to 0.05) p=0.005]*. There was a weak trend towards an association between NE and LE in CR patients *[p=0.180]* and a stronger trend in HN patients *[p=0.061]* so the groups were combined and there was a significant effect overall *[N=61, ß(CI)=0.10 (0.02 to 0.18) p=0.016]* indicating a weak positive association between NE and LE. Those with a PH depression also reported more LE *[N=69, ß(CI)=1.93(0.85 to 3.01) p=0.001]*.

9.2.2 Physiological variables

9.2.2.1 Cortisol and inflammation

Significant findings were as follows:

In CR patients there was a trend towards increased IL6 at T1 in patients with increased 30 minute morning and evening cortisol levels as well as overall mean cortisol. There was also an association between increased evening levels of cortisol and increased IFNγ. In HN patients increased morning cortisol (both waking and 30 minute levels) and overall mean cortisol were associated with decreased levels of IFNγ.

The models were then rerun using bootstrapped standard errors and only the association between overall mean cortisol level and IL6 in CR patients remained significant, and weak evidence of a negative association between IFNγ and waking cortisol in HN patients. However many of the results still showed a trend (see table 9.1).

Group	N	Cytokine	Cortisol measure	Coefficients (CI)	P value
CR	*24*	*IL6 T1*	*Waking +30 mins*	*0.62 (-0.19 to 1.43)*	*0.133*
	25	*IL6 T1*	*PM*	*2.31 (-0.17 to 4.79)*	*0.068*
	25	***IL6 T1***	***Overall mean***	***0.96 (0.06 to 1.87)***	***0.038***
	26	*IFNγ T1*	*PM*	*0.73 (-0.89 to 2.35)*	*0.378*
HN	***26***	***IFNγ T1***	***Waking***	***-0.33 (-0.66 to 0.00)***	***0.049***
	26	*IFNγ T1*	*Waking +30 mins*	*-0.18 (-0.31 to 0.02)*	*0.080*
	27	*IFNγ T1*	*Overall mean*	*-0.30 (-0.61 to 0.01)*	*0.057*

Table 9.1: Relationship between cortisol and inflammation using bootstrapped standard errors.

9.2.2.2 Cortisol and psychosocial variables

There was no evidence towards an association between CT and increased cortisol levels.

Contrary to expectations the only associations were an inverse correlation between NE and the cortisol morning rise in CR patients. This remained significant after bootstrapping *[N=19, ß(CI)=-0.11 (-0.19 to -0.03) p=0.008]*. As this was a singular and counter hypothesis finding it was not investigated further, as noted by the point on multiple testing in section 5.4.3.

No association between number of LE at T3 and baseline cortisol levels were found.

There was no significant association between PH depression and cortisol levels.

9.2.2.3 Inflammation and psychosocial variables

The only marker of inflammation at T1 that was associated with CT was CRP in CR patients, which was still significant after bootstrapping *[N=18, ß(CI)=2.25 (0.14 to 4.36) p=0.036, adjusted R^2=0.42]*. There was also a significant positive association between CT levels and increased TNFα levels at T2 in CR patients, which was still significant using bootstrapping *[N=18, ß(CI)=0.19 (0.03 to 0.33) p=0.007]*. There was also a trend towards an association between T1 TNFα and T1 IL6 and CT in CR patients *[p=0.165, p=0.263 respectively]*. There was no evidence towards a relationship between CT and increased inflammation in HN patients at T1 or T2 and there were no associations between CT and inflammation at T3 in either patient group.

There was no association between NE and inflammation in either patient group.

There was a significant negative correlation between LE at T3 and IL6 and TNFα at T1 in CR patients. These results were not significant when using bootstrapping *[p=0.142, p=0.072 respectively]*.

PH depression was associated with a decrease in IFNγ at T3 in all patients which remained significant after bootstrapping *[N=55, ß(CI)= -1.95 (-3.45 to -0.46) p=0.011]*.

There were no significant associations between baseline depressive symptoms and increased postoperative inflammation or perioperative rise.

9.2.2.4 Psychosocial variables, inflammation and current symptoms

Whilst developing the adjusted models it became apparent that many of the relationships between the variables under investigation and depressive symptoms and QoL were mediated by some symptoms, particularly fatigue and pain. This

section reports the results for associations between the main risk factors used in this study and fatigue and pain partly to confirm the confounding effect and also in order to demonstrate potential mechanisms behind any previous findings.

Psychosocial:

There was a trend towards an association between CT and T1 fatigue in CR patients and a significant association in HN cancer patients. When the two groups were combined there was a significant association between CT and T1 fatigue. There was also a significant association between CT and fatigue at T3 in both cancer groups. The only other significant association was between CT and pain at T3 in HN cancer patients (see table 9.2).

Group	Variable	N	ß(CI)	P value
CR	*Fatigue T1*	*18*	*1.65 (-0.46 to 3.76)*	*0.117*
	Fatigue T3	*20*	*2.02 (0.75 to 3.30)*	*0.004*
HN	*Fatigue T1*	*31*	*0.56 (0.22 to 0.90)*	*0.002*
	Fatigue T3	*31*	*0.34 (0.01 to 0.68)*	*0.044*
	Pain T3	*31*	*0.52 (0.09 to 0.94)*	*0.019*
All	*Fatigue T1*	*49*	*0.50 (0.10 to 0.89)*	*0.015*

Table 9.2: coefficients and p values for associations between CT and fatigue and pain.

In longitudinal analyses in CR cancer patients there was a significant association between CT and fatigue *[N=75(20) 1.54 (0.45 to 2.63), p=0.006]*, but there was no association between CT and pain *[p=0.426]*. There was a significant association between CT and pain and fatigue in HN patients *[N=129(34), ß(CI)=0.49(0.13 to 0.85) p=0.008; N=129(34) ß(CI)=0.30(0.00 to 0.60) p=0.050 respectively]*.

Neuroticism was associated with fatigue at baseline in HN patients and then in both patient groups after treatment. Similarly NE was associated with increased pain at T3 in CR cancer patients and T4 in HN cancer patients and if combined, there was a significant association between NE and pain at both T3 and T4 (see table 9.3).

In longitudinal analyses there was no association between NE and pain in CR patients *[p=0.362]*, but there was an association between NE and fatigue. In HN patients there was an association between NE and pain and fatigue (see table 9.3).

	Variable	N	Coeff (CI)	P value
CR	*Fatigue T3*	*21*	*3.47 (1.66 to 5.27)*	*0.001*
	Fatigue T4	*21*	*3.05 (0.61 to 5.50)*	*0.017*
	Fatigue T5	*18*	*2.69 (0.96 to 4.42)*	*0.005*
	Fatigue overall	*80 (22)*	*2.13 (0.12 to 4.15)*	*0.038*
	Pain T3	*21*	*2.98 (0.29 to 5.66)*	*0.032*
HN	*Fatigue T1*	*37*	*1.82 (0.73 to 2.91)*	*0.002*
	Fatigue T3	*38*	*1.40 (0.04 to 2.77)*	*0.044*
	Fatigue T4	*41*	*2.78 (0.82 to 3.84)*	*<0.0005*
	Fatigue T5	*39*	*1.38 (0.11 to 3.29)*	*0.037*
	Fatigue overall	*155 (41)*	*1.87 (0.94 to 2.80)*	*<0.0005*
	Pain T4	*41*	*1.53 (0.00 to 3.06)*	*0.049*
	Pain overall	*155 (41)*	*1.38(0.10 to 2.67*	*0.035*
All	*Pain T3*	*59*	*1.87 (0.41 to 3.33)*	*0.013*
	Pain T4	*62*	*1.68 (0.30 to 3.07)*	*0.018*

Table 9.3: Coefficients and p values for associations between NE and fatigue and pain.

PH depression was associated with increased fatigue at all time points and increased pain at T3 and T4 in all patients and there was a significant association between PH depression and pain and fatigue in longitudinal analyses (see table 9.4).

Life events were associated with increased fatigue in CR cancer patients at T4 and T5 and in HN patients at all time points. Life events were also associated with increased pain at baseline in HN patients, at T3 in all patients and T4 and T5 in CR patients only. There was also a longitudinal relationship between LE and pain in both cancer groups and a trend towards fatigue in the CR group and a significant association in the HN group (see table 9.5).

Variable	N	Coeff (CI)	P value
Fatigue T1	*70*	*21.76 (5.84 to 37.68)*	*0.008*
Fatigue T3	*67*	*25.95 (11.26 to 40.63)*	*0.001*
Fatigue T4	*63*	*26.95 (11.11 to 42.79)*	*0.001*
Fatigue T5	*60*	*22.01 (1.11 to 42.91)*	*0.039*
Fatigue overall	*260 (76)*	*25.67 (12.67 to 38.36)*	*<0.0005*
Pain T3	*67*	*33.36 (10.03 to 56.69)*	*0.006*
Pain T4	*63*	*31.17 (13.12 to 49.22)*	*0.001*
Pain T5	*60*	*32.53 (5.11 to 59.95)*	*0.021*
Pain overall	*260 (76)*	*32.27 (13.68 to 50.85)*	*0.001*

Table 9.4: Coefficients and p values for associations between PH depression and fatigue and pain.

	Variable	N	Coeff (CI)	P value
CR	*Fatigue T4*	*24*	*5.37 (0.08 to 10.66)*	*0.047*
	Fatigue T5	*22*	*5.18 (1.68 to 8.68)*	*0.006*
	Fatigue overall	*96 (27)*	*3.93(-0.24 to 8.10*	*0.065*
	Pain T3	*25*	*5.76 (-0.18 to 11.70)*	*0.057*
	Pain T4	*24*	*8.95 (2.67 to 15.22)*	*0.007*
	Pain T5	*22*	*6.44 (0.46 to 12.42)*	*0.036*
	Pain overall	*96 (27)*	*4.88(1.46 to 8.30)*	*0.055*
HN	*Fatigue T1*	*41*	*9.13 (4.41 to 13.85)*	*<0.0005*
	Fatigue T3	*44*	*8.22 (4.45 to 12.00)*	*<0.0005*
	Fatigue T4	*39*	*4.76 (-0.06 to 9.57)*	*0.053*
	Fatigue T5	*38*	*6.38 (2.08 to 10.69)*	*0.005*
	Fatigue overall	*162 (45)*	*7.85(4.24 to 11.46)*	*<0.0005*
	Pain T1	*41*	*7.95 (2.37 to 13.53)*	*0.006*
	Pain T3	*44*	*8.96 (3.33 to 14.59)*	*0.003*
	Pain overall	*162 (45)*	*7.27(2.82 to 11.72)*	*0.001*
All	*Pain T3*	*69*	*7.43 (3.43 to 11.43)*	*<0.0005*

Table 9.5: Coefficients and p values for associations between LE and fatigue and pain.

Physiological:

Although the previous analyses have all been stratified by cancer group, the analyses with inflammatory markers was exploratory, and the aim was to look for patterns, in order to help interpret the adjusted models which are presented in

chapter 11. As the relationships between inflammation and symptom reporting may be underpowered in this section, where there were trends towards an association in both groups, the groups were combined.

Initial analyses using robust standard errors suggested that there were significant associations between T1 IFNγ, CRP and T1 fatigue in CR patients. There was also significant association between IL6 and fatigue at T1 when both groups were combined, but no associations between inflammation and pain.

T1 IFNγ and CRP were also positively associated with fatigue at T3 in CR patients, and there were negative associations between IL6, TNFα and IFNγ and pain at T4. Whereas, in HN patients the only associations were between T1 IFNγ and IL6 and pain at T5.

T2 TNFα was associated with pain at T5 in CR patients only, whereas T2 CRP was associated with pain at T3 and T5 in HN patients. However, there were trends towards an association between T2 IL6 and T2 CRP and fatigue at T3, T4 and T5 in both groups of patients, to maximise power the groups were combined. There was a significant association between T2 IL6 and CRP and fatigue when both groups were combined at T3, T4 and T5. TNFα at T2 was also associated with increased fatigue at T5 in CR patients and when both groups were combined. Finally IL6 was positively associated with increased pain at T3 in HN cancer patients and when both groups were combined.

After bootstrapping, the significant findings relating to fatigue were:

- IL6 at baseline was associated with increased fatigue at baseline and at T3 in both patient groups.
- There was also an association between TNFα at T2 and fatigue at T3 and a significant cross sectional association between TNFα and fatigue at T3.

- The most pronounced finding was that IL6 and CRP at T2 were associated with increased fatigue after treatment (T3, T4 and T5) when both patient groups were combined (see table 9.6).

Marker	DV	N	Coeff (CI)	P value
IL6 T1	*Fatigue T1*	*70*	*2.31 (0.15 to 4.47)*	*0.036*
IL6 T1	*Fatigue T3*	*59*	*1.97 (-0.03 to 3.98)*	*0.054*
IL6 T2	*Fatigue T3*	*59*	*1.25 (0.01 to 2.49)*	*0.048*
IL6 T2	*Fatigue T4*	*57*	*1.55 (0.54 to 2.56)*	*0.003*
IL6 T2	*Fatigue T5*	*53*	*1.18 (0.26 to 2.10)*	*0.012*
TNFα T2	*Fatigue T3*	*60*	*3.96 (0.25 to 7.68)*	*0.036*
TNFα T3	*Fatigue T3*	*54*	*5.33 (1.05 to 9.62)*	*0.015*
CRP T2	*Fatigue T3*	*60*	*0.19 (0.05 to 0.32)*	*0.007*
CRP T2	*Fatigue T4*	*58*	*0.18 (0.05 to 0.31)*	*0.005*
CRP T2	*Fatigue T5*	*54*	*0.17 (0.04 to 0.30)*	*0.009*

Table 9.6: Coefficients and p values for associations between fatigue and inflammation using bootstrapped standard errors.

The significant associations between pain and inflammation using bootstrapped standard errors were:

- A significant association between increased IL6 at T2 and greater pain at T3 and at T5 in both patient groups.
- The association between IL6 at T2 and pain at T5 showed a trend in the CR group, was significant in the HN group and when both groups were combined.
- CRP at T2 was associated with pain at T5 to the same degree as the IL6 findings.
- There was also a significant association between TNFα at T2 and pain at T5 in CR patients and CRP at T2 and pain at T3 in HN patients (see table 9.7).

Group	Marker	DV	N	Coeff (CI)	P value
CR	*TNFα T2*	*Pain T5*	*20*	*6.66 (1.28 to 12.04)*	*0.015*
HN	*CRP T2*	*Pain T3*	*37*	*0.22 (0.03 to 0.41)*	*0.026*
All	*CRP T2*	*Pain T5*	*54*	*0.26 (0.11 to 0.41)*	*0.001*
All	*IL6 T2*	*Pain T3*	*59*	*1.23 (0.05 to 2.41)*	*0.041*
All	*IL6 T2*	*Pain T5*	*53*	*1.31 (0.06 to 2.57)*	*0.041*

Table 9.7: Coefficients and p values for associations between pain and inflammation using bootstrapped standard errors.

9.3 Discussion

9.3.1 Psychological variables

Childhood trauma was only weakly associated with NE and was not associated with PH depression. The non significance of these findings is most likely due to low power as many studies have reported a robust relationship between CT, NE and MDD, but most of these have used much larger samples[62, 74, 200, 318]. As expected, NE was associated with a PH of depression and CT, NE and PH depression were all associated with LE. As the BLEQ does not give enough information to assess whether the LE may be partly caused by the individual it is not possible to tell whether this relationship is predominantly effected by dependent LE as suggested by the literature[62, 200, 294].

9.3.2 Physiological variables

There were relatively few significant findings between inflammation and cortisol levels. The only significant association was between increased baseline IL6 levels and increased daytime cortisol mean in CR patients, which is consistent with past correlational findings[85] (reported in section 9.1.2). However, this was not significant in the HN group, despite similar sample sizes. This may be due to the greater spread of IL6 levels in CR patients compared to HN patients (CR IL6 levels range from 0.25 - 14.87 pg/ml, HN IL6 levels range from 0.32-7.92 pg/ml in those that also completed the salivary aspects of the study). The lack of effect is likely to be due to low power and increased noise from the large number of covariates (as demonstrated by this chapter). For instance, presence of a DD or possibly even the presence of a tumour may impair the anti-inflammatory properties of glucocorticoids[295].

9.3.3 Psychological and physiological variables

There were no significant associations between psychosocial variables and cortisol levels. There was no association between NE and cortisol consistent with the results from the meta-analysis based on data from 22 studies[260]. There was also no association between CT and cortisol levels. This is probably due to low power, especially given the mixed findings in previous studies[106, 255]. Unfortunately, the current sample was not large enough to investigate sub groups or adjust for all of the possible covariates. Similarly, there was no significant association between LE and cortisol. Some larger studies also reported null effects[261, 262]. These null effects are perhaps not surprising given the sample size and large number of variables that also affect cortisol levels, such as genetic factors, type, timing and duration of stress, and gender[110].

There were some significant associations between psychological factors and inflammation. Childhood trauma was associated with increased CRP at baseline and increased TNFα at T2, again only in CR patients. There was also a trend towards an association between baseline TNFα and CT in CR patients. Interestingly, there was no association between inflammation and CT in HN patients, or between IL6 and CT in either cancer group. There was a weak trend, though, towards an association between IL6 and CT in CR patients suggesting that the association between IL6 and CT is weaker and therefore non significant due to low power. Interestingly, the findings of an association between CT and inflammation were non significant in the HN patients, which as previously stated probably reflects the heterogeneity of the HN patients compared to the CR patients, thus obscuring any relationships.

In accordance with the cortisol findings there was no association between NE and increased inflammation. In a population study of over 6000 participants reported only a small association between NE and IL6[319], thus identification of any such association would be unlikely in this much smaller sample . Equally, there was no

association between LE and inflammation, probably due to the imprecision of the stress measure and low power. Finally, there was a negative association between PH depression and IFNγ three months after surgery in all patients. Although this may be a chance finding given the low numbers with a PH depression, it is worthy of further investigation given previous reports of a trend towards higher IFNγ levels and increased survival[237] in CR patients. The meta-analysis investigating the relationship between inflammation and DD found no association between IFNγ and MDD, but only four studies were included in the analyses, one of which found a negative association. No studies have looked at the surgical response of IFNγ in those with a current or past DE. Most studies report an increase in inflammation after surgery, which normally returns to baseline within a month[197]. Kudoh and colleagues[137] (2001) reported an inhibited post surgical rise of IL6 and IL8 in depressed patients, but levels of inflammation were monitored only up to three days post surgery: further supporting the need for more research in this area.

There were no associations between increased baseline depressive symptoms and later inflammation. This could be due to low power, especially as the reported cross sectional associations between depressive symptoms and inflammation are less robust then those between DD and inflammation[87]. The findings are also confounded by the mix of psychological and physiological stressors at the time of completing the HADS and blood sampling.

9.3.4 Psychological and physiological variables and symptoms

Many of the investigated variables were associated with increased pain or fatigue in both the CR and HN cancer patients. CT was associated with increased fatigue at T1 and T3 and increased pain at T3. Childhood trauma is an established risk factor for chronic fatigue in otherwise healthy individuals[320], though these findings were based predominantly on investigations using retrospective measures. Childhood trauma has also been associated with increased chronic wide spread pain reporting in a prospective study[321]. Though, intriguingly, those with CT have

also been shown to have decreased experimental pain perception[322]. Also one prospective study did not find an association using a case control follow up of abuse cases that were serious enough to lead to a court hearing[323]. Although, there was an association between retrospective measures of abuse and neglect and pain reporting in the same sample.

Neuroticism was also associated with increased perioperative fatigue (at baseline and one month post surgery) and post treatment pain (at one and three months post surgery) in both patient samples, supporting previous research in HN patients[212, 227] and extending the findings to CR patients. Past history of depression was associated with increased reporting of fatigue and pain throughout, demonstrating a robust effect of increased symptom reporting in those with a past psychiatric history. Number of LE was also associated with increased fatigue at all time points and increased perioperative pain in HN patients (one and three months), and post operative pain in CR patients (at one, three and six months), again demonstrating a close link between psychological stress and symptom perception in cancer patients.

Consistent with past studies increased inflammation was associated with increased post operative fatigue in both patient groups. The most sustained relationship was between IL6 and CRP levels one week post operation and increased fatigue from one month onwards in both cancer patient groups. There was also a relationship between post operative TNFα levels (at one and three months) and fatigue at three months post surgery. The relationship between inflammation and pain reporting was less pronounced, but there remained a relationship between TNFα, IL6 and CRP levels one week post surgery and pain, but only at one and six months. The association between TNFα and pain was only apparent in CR patients at six months, likewise CRP was only associated with increased pain perception at three months in HN patients, but was significantly associated with pain at T5 in both cancer groups. This supports past studies investigating sickness behaviour and inflammation in cancer patients[31]. As with the findings from the previous chapter

relating to HN cancer and QoL (section 8.2.2.3), it should be noted that there was no relationship between inflammation and pain at three months post treatment, despite a relationship at one and six months. Equally, the associations between psychological factors and symptom perception appear most robust at one and six and less so at three months, perhaps suggestive of a more complicated relationship between psychological and physiological factors at three months post operation.

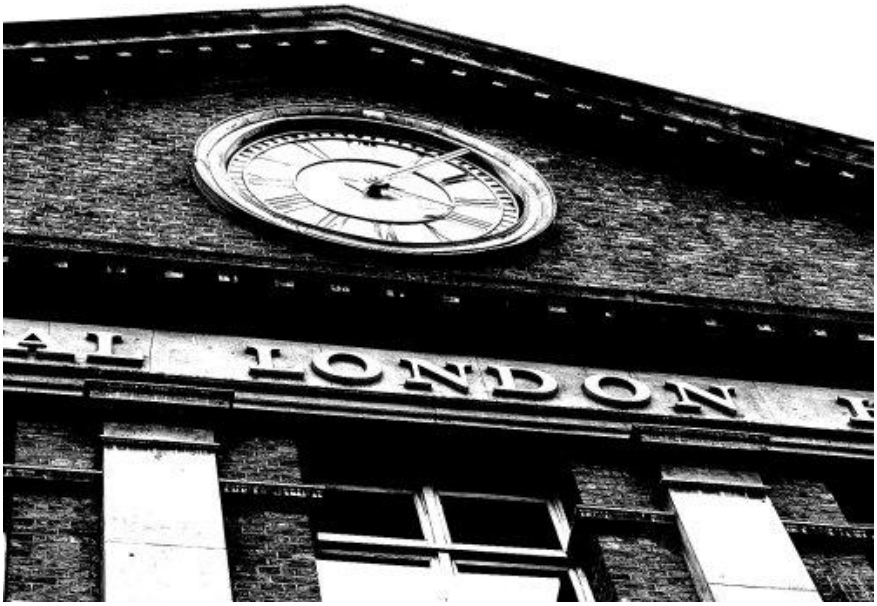
9.3.5 Limitations and Conclusions

The analyses were limited by low power. The findings are based on analyses from a small sample and thus the significant findings require replication and some of the non-significant findings, for which there was a well founded hypothesis, may be significant or more consistent in a larger sample. As a result of low numbers, in some cases the cancer groups were combined, but this also increases the number of factors that may confound the results and obscure any effects. Some of the results may also be chance findings due to the large number of tests that were carried out. This notwithstanding, some strong inter-relationships between psychological and physiological factors were demonstrated emphasizing the importance using multivariate analyses.

This chapter demonstrates that psychological and physiological factors that are associated with increased depressive symptoms, poorer QoL and risk of a DE are also associated with increased symptom perception. The association between psychological factors and pain and fatigue may be partially related to increased vulnerability to sickness behaviour because the psychological factors may potentiate the inflammatory response to cancer and treatment. Although only CT and CRP were significant in this study, it is feasible that the psychological factors increase symptoms and therefore increase the risk of a DE6 through higher cancer symptom burden although it is more likely that there are multiple pathways involved. Also, it should be noted that these findings are based on symptom self-

report measures; therefore it is not possible to say whether the relationship is due to heightened symptom perception or weakened tolerance. As fatigue and pain are closely related to depression, it would also be interesting to test the relationships between the potential markers and more objectively somatic complaints.

In summary, this chapter addressed the fifth hypothesis and the third aim of the thesis: to explore associations between the possible explanatory variables. Thus, this chapter investigated the inter-relationships between psychological and physiological risk markers for depression as well as their relation to self reported symptoms. The results showed that, counter to the hypothesis, there were very few associations between inflammation and cortisol in this sample. The exploratory analyses showed that there were significant inter-relationships between many of the psychological risk factors, as was hypothesised in the literature review. The findings also suggest relationships between many of the psychological variables and some associations between CT and inflammation. Both psychological and physiological variables were associated with increased self reported symptoms in both CR and HN patients. This shows that there is a degree of overlap between the risk factors investigated in the previous chapters with regard to their association with depression and poorer QoL. The next chapter investigates this overlap using multivariate models in order to elucidate the most predictive of the psychological or physiological markers.



10 Adjusted models

Chapters 7 and 8 reported the relationships between the main variables of interest (CT, NE, PH depression, LE, cortisol and inflammation) and depression and QoL. The previous chapter laid out how many of these variables were related to each other and also introduced the relationship between these variables and other symptoms.

So far, many of the investigated variables were related to depressive symptoms and QoL: this chapter consolidates these results to provide final models that address which of the investigated variables are most informative when trying to predict which patients would be at highest risk of increased depressive symptoms, a DE6 or poorer QoL soon after cancer treatment. This chapter also presents adjustments for demographic and cancer related factors, including many of the symptoms in the EORTC-QLQ that were associated with increased depressive symptoms or poorer QoL. This addresses the final aim of the study: to explore the mediating effects of perceived physical symptoms on depressive symptomatology and poorer QoL.

As with the previous chapters, this will comprise a brief literature review followed by the methods section (as the methods in this chapter are unique to this results section) and the results and discussion.

10.1 Background

The rationale for the predictive value of the investigated risk factors and their interrelations was presented in the previous chapters. However, many demographic and cancer related factors are also associated with increased risk of depression and should be taken into account. This review briefly covers what factors are being adjusted for and gives evidence for their association with depression. Although in terms of adjustment, just knowing that a demographic or cancer related variable is associated with the outcome is sufficient justification to include the variable in the model, it may be more relevant to focus on certain variables given the relationship between demographic and lifestyle factors and the chosen psychological and physiological factors under investigation.

Comorbid disability was included as a possible covariate. The demographic and lifestyle factors that were included as possible covariates in the final models were:
Age
Sex
Ethnicity
Marital status
Alcohol consumption
Smoking
BMI
The following cancer related factors were also considered:
TNM staging
Treatment

The measures used are reported in the methods section 6.2.1.

10.1.1 Risk for depression and poorer quality of life

Age was included as a covariate because it is reported to be positively associated with increased depressive symptoms and risk of a DE in the general population[183, 324]. However, a comprehensive review reported the prevalence of MD to be lower than that of younger individuals[325] and the higher levels of depressive symptoms are almost entirely explained by greater prevalence of physical illness and disability[326]. This perhaps explains why increasing age is also associated with increased variability in the levels of depressive symptoms[324]. However, despite this, Schroeff and colleagues[327] (2007) reported that age was not associated with poorer QoL or emotional functioning in a sample of 266 HN cancer patients from diagnosis and up to six years follow up. Sex is included because women are known to be at higher risk of developing mood disorders[59]. Studies investigating gender differences in the prevalence of depression in cancer patients have found mixed results. A review by DeFlorio and Massie[328] (1995) reported that 23 out of 25 studies found no difference between women and men with regard to rates of depression, except in sub types of depression. Ethnicity is also known to influence risk of a DD, where whites, (compared to Hispanics and non-Hispanic Black) are considered to be at greater risk of a mood disorder in an American population[59]. However, Indian and Pakistani individuals have been shown to have higher levels of disorder compared to Whites and Bangladeshis in a British population, and no difference was found between Black Caribbean and White samples[329]. Marriage has also been found to be protective as married individuals show lower levels of depressive symptoms[330]. Similarly, living alone was associated with increased depressive symptoms in a small sample of 107 HN cancer patients[131].

Depression is also associated with several unhealthy lifestyle factors including smoking and alcohol consumption. Alcohol consumption appears to have a J shaped relationship as moderate drinking is associated with lower depressive symptoms than rarely or never drinking[315]. Whereas relatively high alcohol consumption (three or more drinks per day) is also a risk factor for depressed

mood[49] when compared to abstinence. Furthermore there is high comorbidity between alcohol and mood disorders; someone dependent on alcohol is at 3.7x the odds of having a mood disorder compared to someone without alcohol dependence[331]. Smoking is reported to have a bidirectional association with depression; daily smoking increases the risk of a DE at follow up one to five years later, but a baseline DD also increases the odds of starting to smoke by three times that of someone without a DD. Finally, being unhealthily overweight or suffering from a physical disability are also associated with increased depressive symptoms or risk of a DE[49, 69, 332].

As well as the demographic and lifestyle choices associated with depression, the level of depressive symptoms and QoL in cancer patients is also affected by a number of cancer variables. Cancer site has a major influence of QoL and depressive symptoms[186]. Also, patients with more advanced disease are reported to have increased depressive symptoms and poorer QoL[333]. As reviewed in chapter 3, cancer specific problems that interfere with social function as well as and symptoms common to both depression and cancer are likely to have a detrimental effect on QoL and be associated with increased depressive symptoms. Also, as reviewed in chapter 1, multimodal treatment including chemotherapy and radiotherapy are associated with increased symptom burden. Radiotherapy has also been associated with poorer QoL during and after treatment in HN patients, though interestingly it was not associated with lower mood[180], thus HN patients who are treated with adjuvant radiotherapy may have lower QoL at one and three months after surgery compared to those without adjuvant treatment. Radiotherapy is strongly associated with increased fatigue[334], which is reported to cause patients high levels of distress[335].

10.1.2 Relation to investigated variables

Whilst an association with depression or QoL is enough to justify inclusion in a multivariate model, many demographic and cancer related factors are also related

to the variables under investigation in this study, therefore they would be expected to affect the results. This is especially the case when the CR and HN cancer groups are combined and variables that differ between the two groups should be included to check for confounding.

Some psychological risk factors are associated with demographic and lifestyle choices, for example, CT is associated with higher levels of smoking, alcohol consumption and lower physical activity[311, 336] and women tend to show higher levels of NE[337]. Also, as reported in chapter 7, smoking and alcohol consumption are more common in HN patients compared to CR patients due to their involvement in the aetiology of HN cancers. Most intriguingly, many of the demographic and cancer related variables that are associated with increased depressive symptoms and poorer QoL are also associated with increased inflammation. Increasing age has been shown to increase levels of TNFα[338]. Women are reported to have higher levels of IL6, which cannot be accounted for by higher disease burden[314]. Smoking, alcohol consumption and lower physical activity levels are also associated with increased inflammation[315, 339]. Interestingly, as with the association between alcohol consumption and depressive symptoms, the association between alcohol and inflammation also follows a J shaped curve; both high levels of alcohol consumption and never or rarely consuming alcohol are associated with increased CRP when compared to CRP levels in those that drink four or more alcoholic beverages in a week[315, 339]. Increased BMI and comorbid disease are also associated with increased inflammation[91, 338, 340].

The previous chapter demonstrated how the psychological variables and inflammation are related to symptom perception. The majority of studies investigating inflammation in CR and HN cancer patients have also found an association between IL6 and cancer stage[230]. Comorbid disease and stage are also associated with higher levels of IL6 in HN patients[242]. Finally, inflammation

increases in response to surgery[281] and radiotherapy has also been reported to increase inflammation[341].

10.1.3 Conclusions

There is evidence that increasing age, female gender, white ethnicity, being unmarried, greater BMI, TNM staging, alcohol consumption, more comorbid disability, smoking, extensive surgery and adjuvant chemotherapy or radiotherapy would all be expected to be associated with increased depressive symptoms. These factors may moderate or confound the relationship between many of the psychological and physiological markers and are included in this study.

In this study, the paucity of findings relating to cortisol and the questionable reliability of the few significant findings precluded the inclusion of cortisol measures from the multivariate analyses.

Due to the small sample size, not every variable could be included in the model, as this would lead to overfitting and meaningless results. The process of developing each multivariate model is explained in the methods below. Although there is a robust association between demographic and cancer related factors, a study of breast cancer that used multivariate analyses to investigate which variables had the highest association with increased depressive symptoms found that none of the cancer related variables were associated with risk of a DE. The main risk factors were younger age, past psychological treatment and high number of stressful LE other than the cancer diagnosis[214]. Thus, PH depression and LE would be expected to be highly associated with depressive symptoms, poorer QoL and increased risk of a DE6, more so than any of the cancer related variables. However, it was not clear how the relationships between all of the variables and depressive symptoms and QoL would change over the course of the study, as it is possible that symptoms may have more impact soon after diagnosis due to

unfamiliarity with the symptoms and heightened symptomatic burden, or they may have a greater impact later on due to the chronicity of the symptom.

In summary, the previous chapters have focused on key psychological and physiological risk factors that are implicated in the aetiology of depression. This chapter aims to bring those aspects together and investigate which of them is most relevant to the QoL of cancer patients. The rationale for choosing these key psychological and physiological risk factors is described in the respective chapters, this literature review focuses on the multitude of demographic and cancer related variables that are also related to depression and poorer QoL, and are thus also important considerations. Despite the importance of the cancer related variables, those variables that are known to be risk factors for depression in the general population are hypothesised to have the greatest association with depressive symptoms and QoL following a cancer diagnosis.

10.2 Methods

Univariate regression analyses were run between each symptom and demographic or cancer related variable and depressive symptoms or QoL as the dependent variable at each time point for each cancer diagnosis. Only significant variables are reported in the results.

Multivariate models were created using two methods:

The first method started with the significantly associated identified variables reported in the previous chapters. Each model started with the earliest chronologically occurring (significant) risk factor, after which the next chronological risk factor was added (in the order CT, NE, LE, inflammation). In order to meet the assumptions of independence and to maximise power and avoid over adjustment, (especially as the main factors are all interrelated[342]) in instances where the added variable confounded the other variables so that they became non-

significant, the variable with the least explanatory power in the model was dropped. The mediations are reported in the results section. This is especially important in this data set because of the relatively low sample sizes and including too many variables in a regression model (with respect to the number of participants) can lead to instability and inconsistent findings.

Current symptoms (i.e. cross sectional associations) and demographic variables that were found to be significant in the univariate analyses were added to the model in the order of greatest explanatory power, providing they met the inclusion criteria (see note on exclusions in prospective methods section in section 5.5.1). Past history of depression was not included in the final multivariate analyses due to the low frequency of cases. However, where PH depression was significant in univariate analyses it is still included in the description of the development of the model. The list of symptom variables was run through once and any independently significant variables were kept in the model. The list of investigated variables and the symptom list were then run through one more time to check that no dropped items could contribute to the model as well as to check the stability of the model. HADS-A was not included in the model with HADS-D as a dependent variable because depression is usually accompanied by high anxiety and the aim of the multivariate model was to look at prognostic factors and then adjust for cancer related symptoms. Although symptoms such as fatigue may also be due to depression, the HADS-D has no questions relating to fatigue and fatigue could also be a consequence of the cancer or cancer treatment.

Finally, the model was checked for explanatory effects of a core group of variables:
T stage
N stage
Age
Comorbid disability
Sex
For T3 and onwards:

Chemotherapy
Radiotherapy (in HN patients only)
Surgical rating
Baseline HADS-D
Baseline global QoL
For DE6:
Diagnosis

These items were only kept in the model if they were significant in univariate analyses in order to prevent over adjusting, but all confounding effects are reported.

The second method used a stepwise approach as used in the prevalence study (see chapter 3). This was used in order to prevent a bias towards the hypotheses (i.e. that HADS-D explains most of the variance in global QoL scores).

The final models were checked using bootstrapped standard errors and the hypothesised model was compared with the stepwise model. As noted in the main methods section, the number of patients in each model varies due to missing data. The number of patients in the univariate analyses and the final model is reported in each case. If the numbers differed by more than 10 patients, then univariate analyses for each of the variables in the model were run. Univariate analyses were rerun on each variable using only the complete case data (from patients whose data were included in the final model) to check that the relationship was similar to that of the entire sample. If the relationship differed (so that it was non-significant) the results were compared to random samples of the same size.

Again, the models were stratified, except for the model for a DE6, where due to low power the samples had to be combined.

Only T1 inflammation is used in the longitudinal analyses due to model constraints; if the inflammatory variables were entered as longitudinal data then only those time points where both data (inflammatory and questionnaire measures) were available were tested (i.e. at T1 and T3 only). No analyses were conducted using T2 and T3 inflammation because that would have resulted in simultaneous retrospective and prospective analyses.

It is acknowledged that many tests are being conducted on a small sample. These tests were necessary to decipher which variables had the strongest association with depressive symptoms and QoL and therefore which could be most clinically useful. These tests were carried out at each time point to investigate whether the relative associations between symptoms and psychological or physiological factors varied over time, as this was also an important clinical question.

10.3 Results

The results are reported for depressive symptoms, DE6 and QoL in turn: always reporting the findings for CR patients first, followed by HN patients. This chapter also includes schematic models summarising the findings at each time point.

10.3.1 Descriptives for EORTC-QLQ symptoms

Table 10.1 shows the sample size, mean, standard deviation and medians of all of the core EORTC-QLQ scales that were used in the analyses. The level of symptoms is similar in each patient set apart from lower levels of dyspnoea and diarrhoea in the HN patients compared to the CR patients *[N=278(90), ß(CI)=-16.64 (-29.39 to -3.90) p=0.010; N=279(90), ß(CI)=-14.13 (-22.52 to -5.74) p=0.001, respectively]*. There is also a non significant trend towards increased appetite loss in the HN patients compared to the CR patients. Fatigue increases before falling back to near baseline levels in both patients. Levels of insomnia appear to increase in HN patients but decrease in CR patients over time.

Table 10.2 shows the N, mean, standard deviation and median of all the CR29 items used in the study and table 10.3 shows the N, mean, standard deviation and median of all the H&N35 items used in the study.

Mean (sd)	CR								HN							
	T1		T3		T4		T5		T1		T3		T4		T5	
	N		N		N		N		N		N		N		N	
Fatigue	32	36.98 (30.64)	25	41.33 (31.35)	24	43.06 (29.55)	22	31.82 (22.82)	52	26.92 (26.53)	45	35.56 (23.16)	41	33.33 (23.83)	40	30.18 (24.13)
Nausea and vomiting	32	6.77 (16.85)	25	14.67 (22.73)	24	9.72 (16.24)	22	3.79 (7.15)	52	5.13 (12.14)	45	13.33 (24.52)	41	9.35 (15.39)	40	5.83 (10.37)
Pain	32	25.00 (31.68)	25	28.67 (29.08)	24	25.69 (31.84)	22	28.79 (33.01)	52	26.92 (31.34)	45	27.04 (29.79)	41	26.42 (25.27)	40	20.42 (27.34)
Dyspnoea	32	36.46 (37.25)	24	22.22 (27.22)	23	34.78 (36.90)	22	33.33 (39.84)	52	15.28 (25.96)	44	12.88 (20.61)	41	14.63 (22.42)	40	10.83 (19.07)
Insomnia	31	39.78 (37.93)	25	38.67 (36.87)	24	38.89 (34.98)	22	42.42 (38.74)	52	37.18 (34.08)	45	32.59 (31.37)	41	28.46 (33.80)	40	26.67 (29.43)
Appetite loss	32	18.75 (29.26)	25	22.67 (30.00)	24	13.89 (23.91)	22	6.06 (13.16)	52	22.44 (27.79)	45	22.96 (27.36)	41	31.71 (33.29)	40	27.50 (35.32)
Constipation	32	20.83 (35.67)	25	21.33 (38.35)	24	18.06 (31.05)	22	12.12 (26.32)	52	19.87 (28.97)	45	22.86 (29.15)	41	24.39 (28.89)	40	18.33 (31.98)
Diarrhoea	32	25.00 (34.91)	25	13.33 (21.52)	24	15.28 (31.05)	21	9.52 (18.69)	52	2.56 (8.97)	44	12.12 (25.00)	41	6.50 (15.31)	40	2.50 (8.89)
Financial difficulties	32	10.42 (23.09)	25	16.00 (34.85)	24	12.50 (23.70)	20	6.67 (17.44)	52	18.59 (34.56)	44	25.76 (35.85)	41	21.95 (34.65)	37	16.22 (31.05)

Table 10.1: Descriptives for Core EORTC-QLQ scales used in the analyses.

Mean (sd)	T1 N		T3 N		T4 N		T5 N	
Health anxiety*	17	54.90 (31.60)	15	56.67 (32.00)	17	59.80 (30.39)	20	73.33 (11.45)
Body image*	6	94.44 (9.30)	9	79.01 (21.83)	12	79.93 (28.75)	14	79.37 (29.83)
Function								
Sexual function* (♂)	3	55.56 (19.26)	5	66.67 (40.82)	7	61.90 (48.80)	7	61.90 (44.84)
Sexual function* (♀)	3	66.67 (57.74)	3	44.44 (50.92)	4	75.00 (50.00)	5	86.67 (18.26)
Micturition problems	6	33.33 (26.29)	9	27.16 (18.52)	12	21.30 (18.02)	14	19.05 (14.73)
Abdominal/pelvic pain	6	16.67 (20.79)	9	13.58 (18.24)	12	7.40 (10.94)	14	3.97 (8.28)
Defaecation problems	6	30.56 (35.22)	9	6.48 (10.85)	11	9.09 (11.46)	13	9.62 (12.19)
Faecal incontinence	4	33.33 (27.22)	6	22.22 (17.21)	10	18.33 (14.59)	11	15.15 (13.85)
Bloating	16	10.42 (15.96)	15	20.00 (30.34)	17	11.76 (20.21)	20	10.00 (15.67)
Dry mouth	17	27.45 (33.82)	15	22.22 (24.12)	17	15.69 (29.15)	20	18.33 (31.48)
Hair loss	17	1.96 (8.08)	15	6.67 (25.82)	17	7.84 (14.57)	20	8.33 (18.34)
Taste problems	17	7.84 (18.74)	15	20.00 (32.85)	17	15.69 (29.15)	20	10.00 (30.78)
Sore skin	4	25.00 (50.00)	6	11.11 (17.21)	10	10.00 (16.10)	11	15.15 (22.92)
Embarrassment	4	33.33 (47.14)	6	27.78 (28.97)	9	25.93 (32.39)	11	21.21 (34.23)
Stoma problems	0	-	3	11.11 (19.25)	4	16.67 (33.33)	4	8.33 (16.67)
Impotence	3	33.33 (33.33)	4	41.67 (41.94)	5	40.00 (43.46)	5	40.00 (43.46)
Dyspareunia	2	0	2	0	4	0	4	0

Table 10.2: Descriptives for CR29 module of EORTC-QLQ.

Mean (sd)	T1 N		T3 N		T4 N		T5 N	
HN pain	35	25.95 (19.88)	31	26.34 (18.52)	32	31.25 (26.61)	39	16.88 (14.87)
Swallowing difficulties	35	14.05 (22.03)	31	25.81 (23.12)	32	26.82 (29.08)	39	16.31 (21.28)
Problems with taste and smell	35	14.29 (26.86)	31	20.43 (26.07)	32	28.65 (30.60)	39	28.63 (32.21)
Speech problems	35	17.46 (23.38)	30	28.33 (28.60)	29	32.95 (27.29)	38	22.51 (24.16)
Problems with social eating	35	18.33 (25.71)	30	38.70 (32.16)	29	37.36 (37.90)	38	27.41 (30.93)
Problems with social contact	35	10.52 (21.60)	30	20.37 (24.80)	29	18.39 (24.79)	38	14.21 (22.74)
Less sexuality	31	29.03 (37.75)	24	32.64 (37.90)	27	40.12 (40.89)	35	34.29 (40.61)
Problems with teeth	34	26.47 (29.34)	31	35.48 (38.43)	32	30.21 (37.25)	36	32.41 (36.94)
Restricted mouth opening	35	17.14 (28.44)	31	38.71 (41.36)	32	31.25 (37.80)	39	27.35 (34.09)
Dry mouth	34	22.55 (26.87)	31	39.78 (35.92)	32	39.58 (34.33)	39	42.74 (39.70)
Sticky saliva	35	19.05 (24.64)	31	40.86 (37.23)	32	47.92 (33.80)	38	35.09 (39.47)
Coughing	35	22.86 (31.07)	31	27.96 (28.67)	32	41.67 (36.91)	39	26.50 (31.70)
Taking pain killers	35	62.86 (49.02)	30	60.00 (49.83)	29	41.38 (50.12)	38	39.47 (49.84)
On nutritional supplements	35	34.29 (48.16)	30	53.33 (50.74)	29	51.72 (50.85)	38	50.00 (50.67)
Presence of feeding tube	35	5.71 (23.55)	30	23.33 (43.02)	29	24.14 (43.55)	38	10.53 (31.10)
Weight loss	35	42.86 (50.21)	29	48.28 (50.85)	27	22.22 (42.37)	38	21.05 (41.32)
Weight gain	35	5.71 (23.55)	29	17.24 (38.44)	27	37.04 (49.21)	37	27.03 (45.02)

Table 10.3: Descriptives for H&N35 EORTC-QLQ module.

10.3.2 T1: Depressive symptoms at baseline

10.3.2.1 CR model (T1 HADS-D)

Only fatigue and sex were independently associated with HADS-D at T1 in CR patients (see figure 10.1 and table 10.5).

Univariate associations (N)
PH depression
Trend towards NE (21)
T1 EORTC-QLQ symptoms:
Sore skin (4)
Embarrassment (4)
Defaecation problems (6)
Abdominal or pelvic pain (6)
Problems with taste and smell (17)
Fatigue (32)
Nausea and vomiting (32)
Hair loss (17)
Sex (being female) (33)
HADS-A (33)

Table 10.4: Univariate associations between variables and T1 HADS-D. Symptoms are in order of R^2 value.

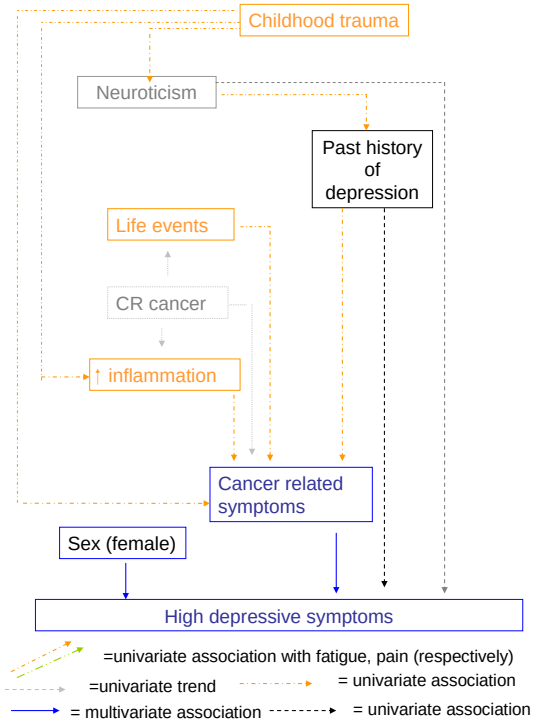


Figure 10.1: Variables associated with HADS-D at baseline in CR cancer patients.

Variable	N	ß (CI)	P value	Adjusted R^2
Fatigue	*32*	*0.07 (0.02 to 0.12)*	*0.009*	*0.40*
Sex		*2.52 (0.33 to 4.71)*	*0.025*	

Table 10.5: Coefficients and p values for all variables associated with baseline HADS-D in CR patients.

10.3.2.2 CR model workings (T1 HADS-D)

- Table 10.4 shows the variables univariately associated with HADS-D at T1.
- Starting with NE and PH, entering sex into the model reduced the relationships between NE and PH and depressive symptoms so that they became non-significant and sex was the only hypothesised variable entered into the symptom adjusted model. Fatigue was the only additional variable that was independently significantly associated with HADS-D.
- Adding T stage, N stage, age, comorbid disability or chemotherapy did not change the model. The model did not change when using bootstrapping and using a stepwise approach generated the same results.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.2.3 HN model workings (T1 HADS-D)

- Table 10.6 shows univariate associations with T1 HADS-D in HN cancer patients
- PH depression and LE were no longer significant when adjusted for CT and NE, and CT was no longer significant after adjusting for fatigue.
- None of the other symptoms were significant.
- None of the demographic or cancer related variables changed the model. Sex was significantly related to HADS-D in the model, showing males were at increased risk of higher depressive symptoms, but sex wasn't significant in univariate analyses and the relationship is in the opposite direction to previous findings, thus it is not included in the final model.
- The model was still significant when using bootstrapped standard errors and the same model was reached when using a stepwise approach.
- Univariate post-hoc analyses indicated no biases in the complete case sample.

10.3.2.4 HN model (T1 HADS-D)

Only fatigue and NE were significantly independently associated with HADS-D at baseline in HN patients (see table 10.7 and figure 10.2)

Univariate associations (N)
CT (32)
NE (38)
LE (42)
PH depression
T1 EORTC-QLQ symptoms:
Fatigue (52)
Insomnia (52)
Pain (52)
Weight loss (35)
Dyspnoea (52)
Nausea and vomiting (52)
Teeth problems (34)
Appetite loss (52)
Constipation (52)
Financial difficulties (52)
HADS-A (53)

Table 10.6: Univariate associations between variables and T1 HADS-D in HN patients. EORTC-QLQ variables are in order of R^2.

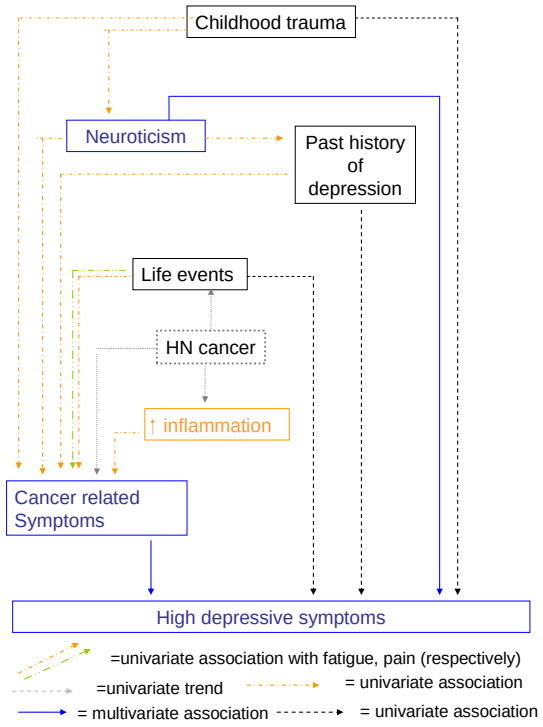


Figure 10.2: Variables associated with HADS-D at baseline in HN cancer patients.

Variable	N	ß (CI)	P value	Adjusted R^2
Fatigue	*37*	*0.08 (0.03 to 0.12)*	*0.001*	*0.47*
NE		*0.20 (0.05 to 0.36)*	*0.012*	

Table 10.7: Coefficients and p values for variables associated with baseline HADS-D in HN patients.

10.3.3 T3: Depressive symptoms at one month post treatment

10.3.3.1 CR model (T3 HADS-D)

Only NE and T1 TNFα were independently significantly associated with HADS-D at T3 (see table 10.9 and figure 10.3).

Univariate associations (N)
CT (20)
NE (21)
T1 TNFα (21)
PH depression
T3 EORTC-QLQ symptoms:
Fatigue (25)
Constipation (25)
Problems with micturition (9)
Appetite loss (25)
Bloating (15)
Pain (25)
Health anxiety (15)
Increasing age

Table 10.8: Univariate associations between variables and T3 HADS-D in CR patients. EORTC-QLQ variables are in order of R^2.

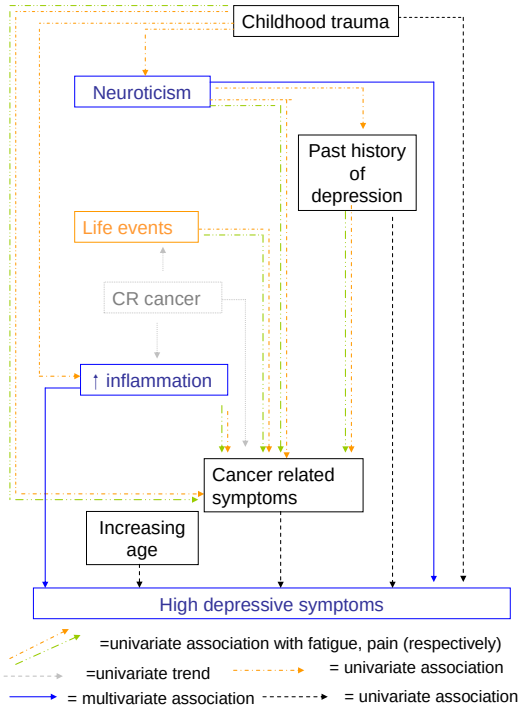


Figure 10.3: Variables associated with HADS-D at T3 in CR patients.

Variable	N	ß (CI)	P value	AdjustedR^2
NE	*18*	*0.52 (0.32 to 0.72)*	*<0.0005*	*0.76*
T1 TNFα		*1.11 (0.71 to 1.50)*	*<0.0005*	

Table 10.9: Variables associated with HADS-D at T3 in CR patients

10.3.3.2 CR model working (T3 HADS-D)

- Table 10.8 shows the variable univariately associated with T3 HADS-D in CR patients.
- PH depression was no longer significant when controlling for NE and CT.
- TNFα at T2 and CT were no longer significant when controlling for TNFα at T1, thus the only hypothesised variables to be independently associated with HADS-D at T3 were NE and T1 TNFα.
- None of the symptom variables were still significant when controlling for NE and T1 TNFα.
- None of the main covariates affected the model. The model was still significant when using bootstrapped standard errors and adjusting for baseline HADS-D or global QoL did not change the model. This model is the same as the stepwise derived model.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.3.3 HN model workings (T3 HADS-D)

- Table 10.10 shows the variables univariately associated with HADS-D at T3 in HN cancer patients.
- Increased number of LE was the only investigated variable independently associated with HADS-D at T3.
- Pain and constipation were the only symptoms positively associated with HADS-D and weight gain was also significantly negatively associated. Diarrhoea was excluded because only three patients scored greater than zero on the scale.
- None of the demographic or cancer related variables affected the model.
- Adding baseline HADS-D to the model reduced the association between weight gain and depressive symptoms.
- All the variables were still significant when using bootstrapped standard errors, but using a stepwise approach resulted in a slightly different model. However, that model was confounded by many other variables, suggesting that it was under powered.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.3.4 HN model (T3 HADS-D)

The final model included LE, pain, constipation and weight gain (see table 10.11 and figure 10.4).

Univariate associations (N)
CT (31)
PH depression
LE (44)
T3 EORTC-QLQ symptoms:
Fatigue (45)
Pain (45)
speech problems (30)
difficulty with social contact (30)
difficulty with social eating (30)
constipation (45)
dry mouth (31)
less sexuality (24)
insomnia (45)
nutritional supplements (30)
senses problems (31)
dyspnoea (44)
sticky saliva (31)
weight loss (29
diarrhoea (44)
presence of feeding tube (30)
nausea and vomiting (45)
swallowing difficulties (31)
weight gain (protective) (29)
Alcohol abuse (42)

Table 10.10: Univariate associations between variables and T3 HADS-D in HN patients. EORTC-QLQ variables are in order of R^2.

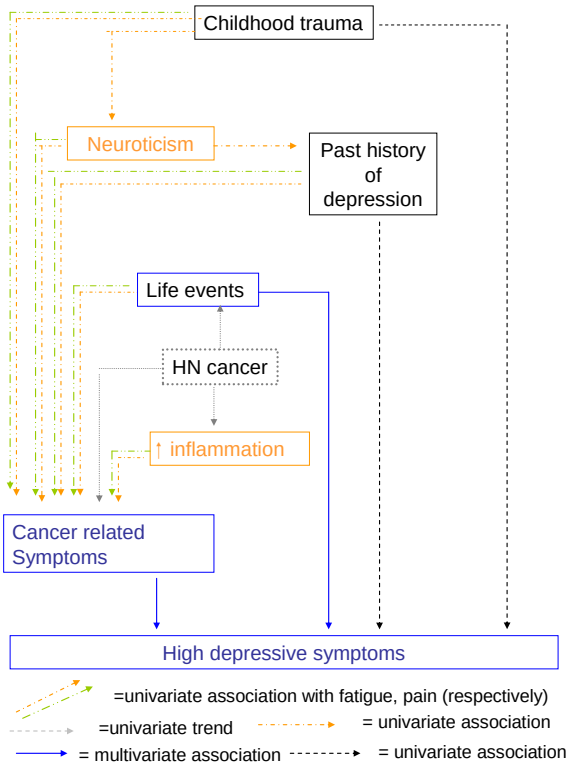


Figure 10.4: Variables associated with HADS-D at T3 in HN patients.

Variable	N	ß (CI)	P value	Adjusted R^2
LE	*28*	*1.08 (0.62 to 1.54)*	*<0.0005*	*0.77*
Pain		*0.04 (0.01 to 0.06)*	*0.004*	
Constipation		*0.05 (0.03 to 0.07)*	*<0.0005*	
Weight gain		*-0.03 (-0.04 to -0.01)*	*0.002*	

Table 10.11: Coefficients and p values for variables significantly and independently associated with HADS-D at T3.

10.3.4 T4: Depressive symptoms at three months post treatment

10.3.4.1 CR model (T4 HADS-D)

CT, NE, financial difficulties and fatigue were the only variables significantly independently associated with HADS-D at T4 in CR patients (see table 10.13 and figure 10.5).

Univariate associations (N)
CT (20)
PH depression
NE (21)
T1 TNFα (21)
T2 TNFα (23)
T4 EORTC-QLQ symptoms:
Impotence (5)
Health anxiety (17),
Loss of libido (m, 7)
Body image (12),
Financial difficulties (24)
Constipation (24)
Insomnia (24),
Problems with taste and smell (17)
Fatigue (24)
Current alcohol consumption (19)

Table 10.12: Univariate associations between variables and T4 HADS-D in CR patients. EORTC-QLQ variables are in order of R^2. m=male.

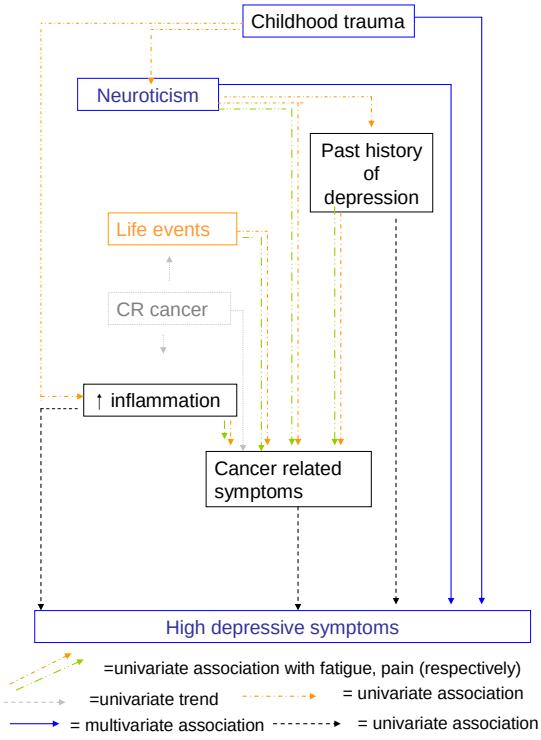


Figure 10.5: Variables associated with HADS-D at T4 in CR cancer patients.

Variable	N	ß (CI)	P value	Adjusted R^2
CT	*19*	*0.31 (0.13 to 0.48)*	*0.002*	*0.71*
NE		*0.25 (0.02 to 0.48)*	*0.037*	
Financial difficulties		*0.05 (0.00 to 0.09)*	*0.038*	
Fatigue		*0.03 (0.01 to 0.06)*	*0.009*	

Table 10.13: Variables associated with HADS-D at T4 in CR patients.

10.3.4.2 CR model workings (T4 HADS-D)

- Table 10.12 shows the variables univariately associated with HADS-D at T4.
- Impotence, health anxiety, body image and problems with taste and smell were excluded due to low numbers.
- PH depression has a greater association than NE, but was excluded from the multivariate model due to the low numbers.
- TNFα at T1 or T2 were no longer significantly associated with depressive symptoms when controlling for CT, NE, or alcohol consumption, thus only CT and NE were used in the fully adjusted model.
- Financial difficulties and fatigue were the only other variables independently associated with HADS-D at T4.
- T stage confounded the relationship between financial difficulties and depressive symptoms, but this is likely to be due to suppression as T stage was inversely associated with depressive symptoms. Chemotherapy, comorbid disability and age all reduced the association between fatigue and HADS-D, but were not significant factors in the model. Similarly sex confounded NE, and surgical rating confounded financial difficulties, but neither was significant.
- Adjusting for baseline depressive symptoms did not change the model. Childhood trauma was not significant when bootstrapped, this may be due to the very low numbers.
- The final model is the same as when using a stepwise approach.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.4.3 HN model working (T4 HADS-D)

- Table 10.14 shows the variables univariately associated with HADS-D at T4
- PH depression and LE were no longer significant when adjusting for NE
- The only significant symptom variable was problems with social contact (although less sexuality also fitted in the model in place of social contact).
- None of the demographic or cancer related variables changed the model, except from comorbid disability which confounded social contact and baseline HADS-D which confounded NE.
- All of the variables were still significant when using bootstrapped standard errors and the same model was reached when using a stepwise approach.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.4.4 HN model (T4 HADS-D)

Only NE and problems with social contact were significantly associated with increased depressive symptoms at T4 in HN patients (see table 10.15 and figure 10.6).

Univariate associations (N)
NE (41)
LE (40)
PH depression
T4 EORTC-QLQ symptoms:
Social contact (29)
Less sexuality (27)
Fatigue (41)
Appetite loss (41)
Speech problems (29)
Problems with senses (32)
Problems with social eating (29)
Insomnia (41)
Constipation (41)
T stage (41)

Table 10.14: Univariate associations between variables and T4 HADS-D in CR patients. EORTC-QLQ variables are in order of R^2.

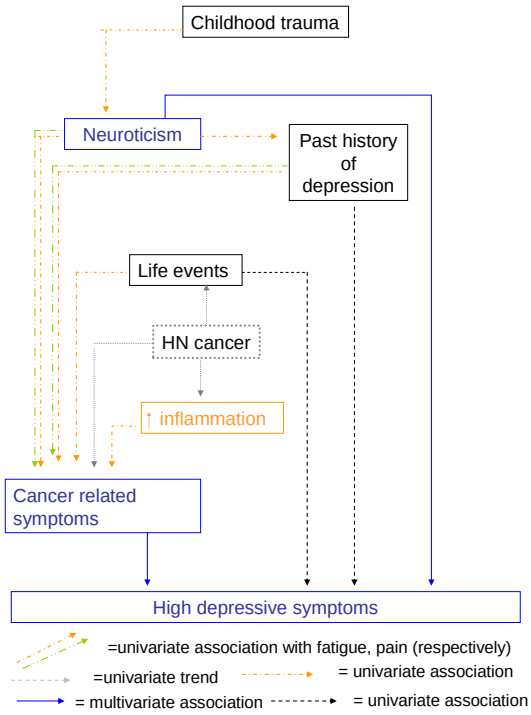


Figure 10.6: Variables associated with HADS-D at T4 in HN cancer patients.

Variable	N	ß (CI)	P value	Adjusted R2
Problems with social contact	*29*	*0.09 (0.04 to 0.14)*	*0.001*	*0.52*
NE		*0.22 (0.03 to 0.41)*	*0.027*	

Table 10.15: Variables associated with HADS-D at T4 in HN patients.

10.3.5 T5: Depressive symptoms at six months post treatment

10.3.5.1 CR model (T5 HADS-D)

Only CT and diarrhoea were independently associated with T5 HADS-D in CR patients (see table 10.17 and figure 10.7).

Univariate associations (N)
CT (18)
NE (18)
Perioperative CRP (18)
PH depression
T5 EORTC-QLQ symptoms:
Impotence (5)
Fatigue (22)
Dry mouth (20)
Diarrhoea (21)
Problems with taste (20)
Health anxiety (20)
Hair loss (20)
Alcohol consumption (18)

Table 10.16: Univariate associations between variables and T5 HADS-D in CR patients. EORTC-QLQ variables are in order of R^2.

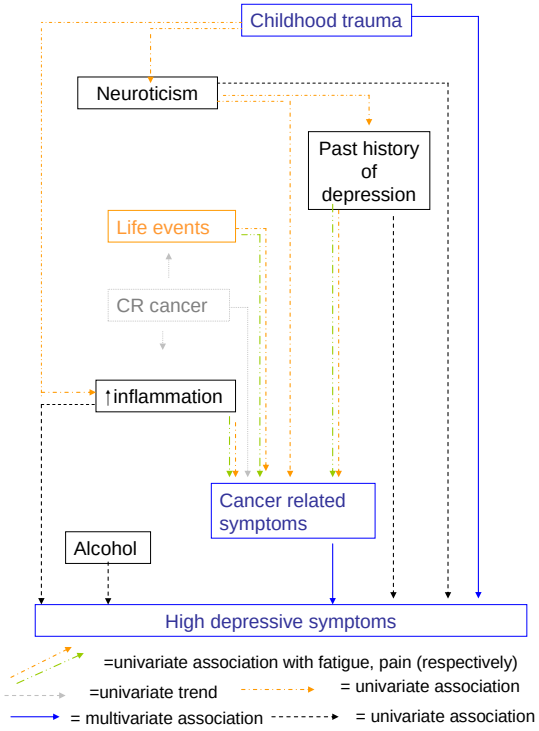


Figure 10.7: Variables associated with HADS-D at T5 in CR patients.

Variable	N	ß (CI)	P value	Adjusted R^2
Diarrhoea	*17*	*0.09 (0.03 to 0.15)*	*0.006*	*0.56*
CT		*0.32 (0.04 to 0.61)*	*0.030*	

Table 10.17: Variables associated with HADS-D at T5 in CR patients.

10.3.5.2 CR model working (T5 HADS-D)

- Table 10.16 shows the variables univariately associated with HADS-D at T5 in CR cancer patients.
- Neuroticism, PH depression, CRP and alcohol consumption were no longer significant after controlling for CT.
- When adjusting for symptoms CT and fatigue were equally associated with HADS-D but collinear.
- Only diarrhoea was independently associated with HADS-D at T5. Thus the final model included either CT and diarrhoea or fatigue and diarrhoea. CT was chosen as a baseline variable is more clinically useful. However, only five pts scored greater than zero on the diarrhoea scale.
- Neither adjusting for the core covariates nor using bootstrapping affected the model. Inserting T1 HADS-D into the model mediated the association between fatigue and T5 HADS-D, but not CT. Using a stepwise approach derived the same model.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.5.3 HN model working (T5 HADS-D)

- Table 10.18 shows the variables univariately associated with HADS-D at T5 in HN cancer patients.
- Childhood trauma, PH depression and LE were non-significant when adjusting for NE.
- Neuroticism was no longer significant after adjusting for fatigue.
- Childhood trauma was still significant even when adjusting for fatigue.
- The only other symptom was lower sexuality.
- Childhood trauma was confounded by comorbid disability and baseline HADS-D, but no other demographic or cancer related variables affected the model.
- All variables were still significant when using bootstrapped standard errors and the same model was come to when using a stepwise approach.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.5.4 HN model (T5 HADS-D)

Thus only CT, fatigue and less sexuality were significantly independently associated with HADS-D at T5 in HN patients (see table 10.19 and figure 10.8).

Univariate associations (N)
CT (33)
NE (39)
PH depression
LE (39)
T5 EORTC-QLQ symptoms:
Less sexuality (35)
Fatigue (40)
Speech problems (38)
Problems with social contact (38)
Pain (40)
Insomnia (40)
Problems with senses (39)
Coughing (39)
Constipation (40)
Problems with social eating (38)
T stage (40)

Table 10.18: Univariate associations between variables and T5 HADS-D in HN patients. EORTC-QLQ variables are in order of R^2.

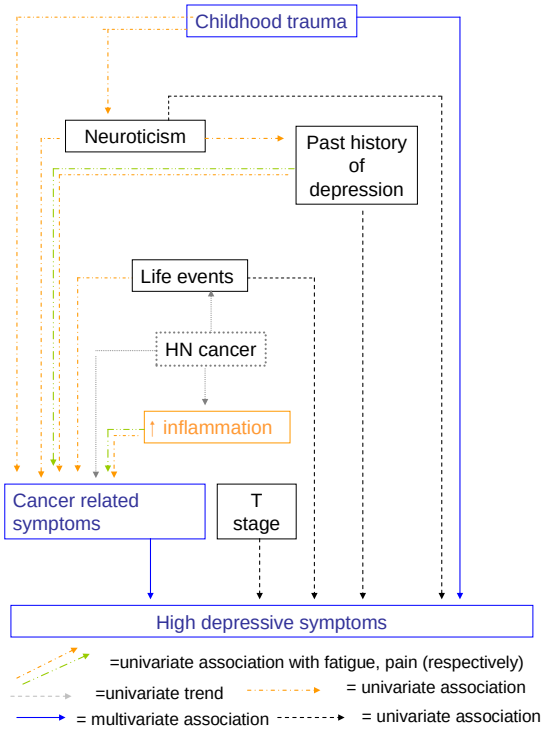


Figure 10.8: Variables associated with HADS-D at T5 in HN patients.

Variable	N	ß (CI)	P value	Adjusted R^2
Less sexuality	*29*	*0.03 (0.01 to 0.05)*	*0.014*	*0.60*
Fatigue		*0.06 (0.04 to 0.09)*	*<0.0005*	
CT		*0.07 (0.01 to 0.13)*	*0.052*	

Table 10.19: Variables associated with HADS-D at T5 in HN patients.

10.3.6 Longitudinal analysis: depressive symptoms at all time points

10.3.6.1 CR model (overall HADS-D)

Neuroticism, LE, fatigue and constipation were the only variables significantly independently associated with HADS-D in CR patients (see table 10.21 and figure 10.9).

Univariate associations (N)
CT (20)
NE (22)
PH depression
LE (27)
Overall EORTC-QLQ symptoms:
Fatigue (34)
Impotence (7)
Stoma problems (5),
Loss of libido (m, 8)
Nausea and vomiting (34)
Micturition (16)
Body image (16)
Constipation (34)
Problems with taste (26)
Financial difficulties (34)
T stage (34)

Table 10.20: Univariate associations between baseline variables and overall HADS-D in CR patients. EORTC-QLQ variables are in order of R^2.

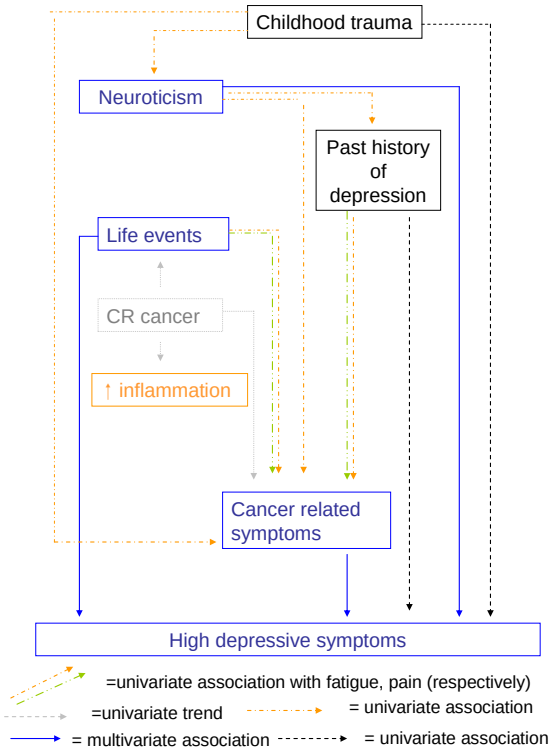


Figure 10.9: Variables associated with HADS-D overall in CR patients.

Variable	N	ß (CI)	P value	Between R^2
Fatigue	*22*	*0.03 (0.00 to 0.07)*	*0.038*	*0.79*
Constipation		*0.03 (0.01 to 0.06)*	*0.003*	
LE		*0.52 (0.24 to 0.79)*	*<0.0005*	
NE		*0.18 (0.07 to 0.28)*	*0.001*	

Table 10.21: Variables associated with HADS-D in CR patients.

10.3.6.2 CR model working (overall HADS-D)

- Table 10.25 shows the baseline variables associated with overall HADS-D.
- Micturition problems and body image were both significant in the multivariate model, but were excluded due to low numbers, along with impotence, stoma problems, problems with sexual function, and taste problems.
- Childhood trauma was no longer significant when adjusting for LE and PH depression was no longer significant after adjusting for NE, thus only NE and LE were entered into the final model.
- After adding the remaining symptoms only fatigue and constipation were significantly independently associated with increased HADS-D.
- Chemotherapy, T stage and N stage were all associated with decreased depressive symptoms when added to the model, despite no univariate association.
- As there results were counter to any univariate findings and did not change the rest of the model the findings they were probably due to over fitting.
- Comorbid disability, surgical rating and age confounded the relationship between fatigue and HADS-D, but were not significant in the model.
- All the variables in the model were also significant when bootstrapped and the model was the same as the stepwise generated model.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.6.3 HN model working (overall HADS-D)

- Table 10.22 shows the variables univariately associated with overall HADS-D.
- PH depression was no longer significant after adjusting for NE and CT was no longer significant after adjusting for LE and LE was no longer significant after adjusting for fatigue.
- The only other symptoms independently associated with HADS-D were less sexuality and diarrhoea.
- None of the core set of covariates affected the model and all the variables included were still significant when using bootstrapped standard errors and the same set was derived when using a stepwise approach.
- Univariate post hoc analyses indicated no biases in the complete case sample.

10.3.6.4 HN model (overall HADS-D)

The only variables significantly and independently associated with increased depressive symptoms in HN patients were fatigue, NE, less sexuality and diarrhoea (see table 10.23 and figure 10.10).

Univariate associations (N)
CT (34)
NE (41)
PH depression
LE (45)
Overall EORTC-QLQ symptoms:
Fatigue (56)
Pain (56)
Insomnia (56)
Problems with social contact (51)
Constipation (56)
Dyspnoea (56)
Less sexuality (49)
Speech problems (51)
Problems with social eating (51)
Nausea and vomiting (56)
Problems with senses (51)
Nutritional supplements (51)
Appetite loss (56)
Financial difficulties (56)
Dry mouth (50)
Weight loss (51)
Difficulty swallowing (51)
Sticky saliva (51)
Restricted mouth opening (51)
Use of feeding tube (51)
Diarrhoea (56)
HADS-A (56)

Table 10.22: Univariate associations between variables and overall HADS-D in HN cancer patients. EORTC-QLQ variables are in order of R^2.

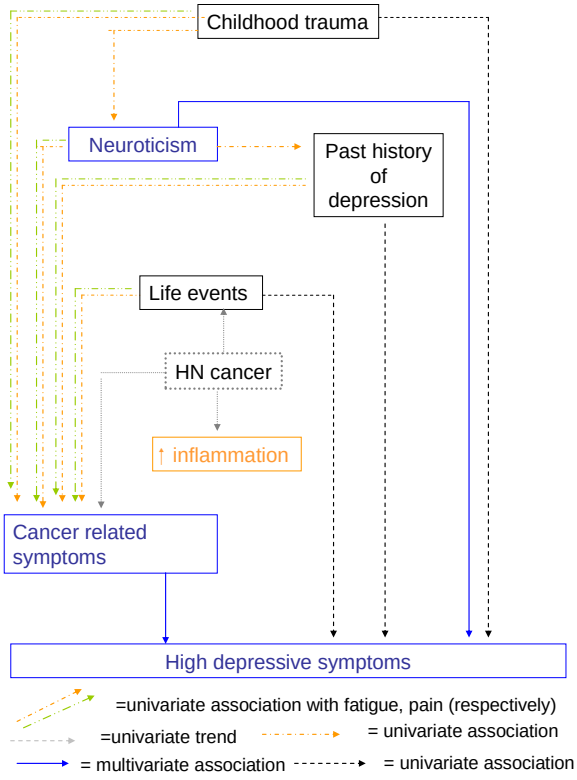


Figure 10.10: Variables associated with HADS-D overall in HN patients.

Variable	N	ß (CI)	P value	Between R^2
Fatigue	*38*	*0.06 (0.03 to 0.09)*	*<0.0005*	*0.56*
NE		*0.15 (0.02 to 0.29)*	*0.025*	
Less sexuality		*0.02 (0.01 to 0.04)*	*0.006*	
Diarrhoea		*0.04 (0.01 to 0.06)*	*0.015*	

Table 10.23: Variables associated with HADS-D in HN patients.

10.3.7 Depressive episode

10.3.7.1 Using baseline data

PH depression, NE and LE were the only factors independently associated with increased risk of a DE6 in HN or CR cancer patients (see table 10.25 and figure 10.11).

Univariate associations (N)
PH depression (65)
NE (60)
LE (63)
T1 HADS-D (66)
T1 EORTC-QLQ symptoms:
Fatigue (60)
Insomnia (59)
Global QoL (60)

Table 10.24: Univariate associations between baseline variables and DE6. EORTC-QLQ variables are in order of R^2.

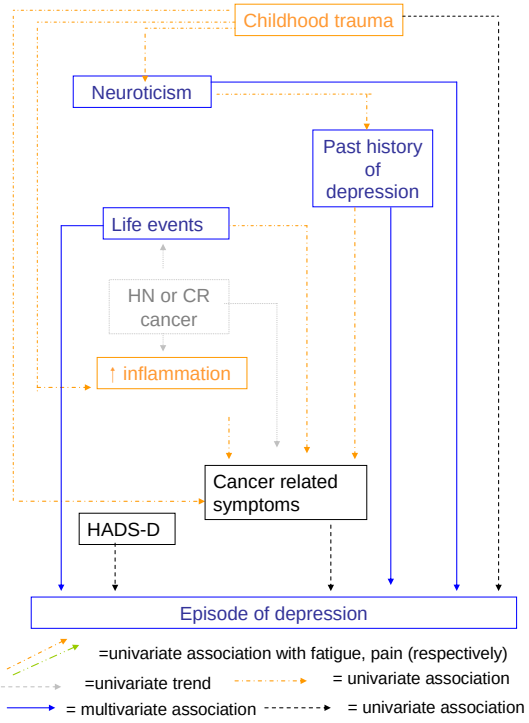


Figure 10.11: Baseline variables associated with a DE6.

Variable	N	OR (CI)	P value	Between R^2
PH depression	*58*	*23.41 (2.88 to 190.20)*	*0.003*	*0.59*
NE		*1.48 (1.07 to 2.06)*	*0.019*	
LE		*1.76 (1.06 to 2.91)*	*0.028*	

Table 10.25: Baseline variables associated with increased risk of a DE6.

10.3.7.2 Baseline model workings

- Table 10.24 shows the baseline variables associated with increased odds of a DE6.
- Past history of depression, NE and LE were all independently associated with a DE whereas none of the baseline symptoms or alcohol abuse were.
- Increasing age (N=66) was also a significant risk factor when added to the model (but not univariately associated) but did not change the strength of the other associations.
- Diagnosis, sex and comorbid disability all confounded LE but were not significant.
- As with the depression findings in the previous chapter, using bootstrapped standard errors reduced all findings to non significant effects. Using a stepwise approach derived the same model.
- Univariate post-hoc analyses indicated no biases in the complete case sample.

10.3.7.3 Longitudinal analyses workings

The analyses were rerun using longitudinal analyses as the longitudinal analyses allow inclusion of the repeated symptom measures which may give a better representation of the symptoms than using only baseline scores.

- Table 10.26 shows the variables univariately associated with a DE6.
- Alcohol abuse was excluded as no CR patients had a PH of alcohol abuse.
- In this model HADS-D was no longer significant after adjusting for PH depression and T stage and age were no longer significant after adjusting for surgical rating.
- No other variables in the core set of covariates confounded the relationships, including diagnosis
- As before, nothing was significant when using bootstrapped standard errors, but the same model was derived when using a stepwise approach.

10.3.7.4 Longitudinal analyses

Only PH depression, NE, LE and surgical rating were independently significantly associated with DE6 when using longitudinal analyses (see table 10.27 and figure 10.12).

Univariate associations (N)
PH depression (65)
NE (60)
LE (63)
T1 HADS-D (66)
T stage (65)
N stage (62)
Increasing age (protective) (66)
Surgical rating (60)
Alcohol abuse (65)

Table 10.26: Univariate associations between baseline variables and DE6. EORTC-QLQ variables are in order of R^2.

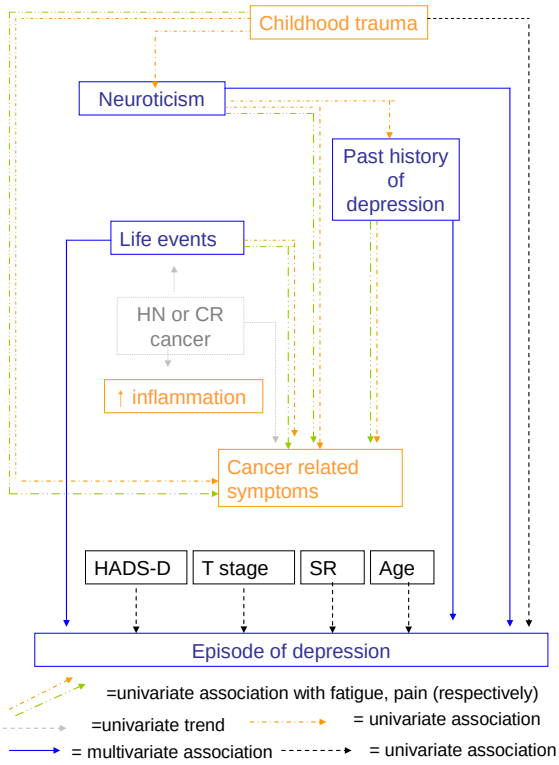


Figure 10.12: Variables associated with a DE6. SR=surgical rating.

Variable	N	ß (CI)	P value
PH depression	*260 (52)*	*17.55 (11.56 to 23.54)*	*<0.0005*
NE		*2.15 (1.38 to 2.92)*	*<0.0005*
LE		*5.55 (2.99 to 8.10)*	*<0.0005*
Surgical rating		*1.91 (0.13 to 3.68)*	*0.035*

Table 10.27: Coefficients and P values for variables associated with DE within 6 months using longitudinal modelling.

10.3.8 T1: QoL at baseline

The same set of analyses as used previously with depressive symptoms and DE6 were also carried out using global QoL as an outcome. It was of interest to find out which variables were most strongly associated with poorer QoL at each time point, as this may differ from depressive symptoms.

10.3.8.1 CR model (T1 QoL)

HADS-D, T stage and fatigue were the only variables associated with poorer QoL at baseline in CR cancer patients. Please see univariate associations in table 10.28, unadjusted model in table 10.29 and adjusted model in table 10.30.

Univariate associations (N)
HADS-D (32)
T1 TNFα (27)
T1 EORTC-QLQ symptoms:
Faecal incontinence (4)
Abdominal/pelvic pain (6)
Health anxiety (17)
Pain (32)
Dry mouth (17)
Taste problems (17)
Appetite loss (32)
Nausea and vomiting (32)
Constipation (32)
Dyspnoea (32)
Insomnia (31)
Hair loss (17)
HADS-A (32)
Trend T stage (32)

Table 10.28: Univariate associations between baseline variables and T1 QoL. EORTC-QLQ variables are in order of R^2.

- Faecal incontinence, abdominal/pelvic pain, hair loss and defaecation problems were not included in the final model due to low numbers.
- Fatigue was not significant after adjusting for TNFα.
- Adjusting for N stage, age, comorbid conditions and sex did not change the model.
- TNFα was no longer significant after adjusting for T stage.
- All models were the same when bootstrapped and fit with the stepwise generated model.

Variable	N	ß (CI)	P value	Adjusted R^2
HADS-D	*27*	*-5.00 (-6.23 to -3.76)*	*<0.0005*	*0.71*
T1 TNFα		*-2.87 (-5.01 to -0.73)*	*0.011*	

Table 10.29: Unadjusted coefficients and p values for variables independently associated with QoL at baseline.

Variable	N	ß (CI)	P value	Adjusted R^2
HADS-D	*32*	*-4.23 (-5.68 to -2.78)*	*<0.0005*	*0.70*
T stage		*-0.19 (-0.36 to -0.02)*	*0.031*	
Fatigue		*-8.62 (-14.07 to -3.17)*	*0.003*	

Table 10.30: Adjusted coefficients and p values for variables independently associated with QoL at baseline.

10.3.8.2 HN model (T1 QoL)

The only variables independently associated with baseline global QoL were fatigue, nausea and vomiting, T stage and problems with social eating (see table 10.32).

Univariate associations (N)
Neuroticism (37)
LE (41)
PH depression
HADS-D (52)
T1 EORTC-QLQ symptoms:
Social contact (35)
Fatigue (52)
Pain (52)
Dyspnoea (52)
Nausea and vomiting (52)
Constipation (52)
Feeding tube (35)
Weight loss (35)
Nutritional supplements (35)
Social eating problems (35)
Less sexuality (31)
Financial difficulties (52)
Speech problems (35)
Appetite loss (52)
Insomnia (52)
Teeth problems (34)
HADS-A (52)
T stage (52)
Current alcohol consumption (41)
Lack of partner (50)

Table 10.31: Variables univariately associated with poorer QoL at baseline in HN cancer patients. EORTC-QLQ symptoms are presented in order of R^2.

- Use of feeding tube was not included in the multivariate model because only two patients were using a feeding tube.
- Neuroticism, LE, HADS-A and PH depression were no longer significant after adjusting for HADS-D.
- HADS-D was no longer significant after adjusting for fatigue.
- N stage confounded social eating. Comorbid disability confounded T stage and social eating.
- All of the variables were still significant when using bootstrapped standard errors and the model was similar to the model derived using stepwise methods.

Variable	N	ß (CI)	P value	Adjusted R^2
Fatigue	*35*	*-0.46 (-0.65 to -0.28)*	*<0.0005*	*0.75*
Nausea/Vomiting		*-0.71 (-1.10 to -0.32)*	*0.001*	
T stage		*-4.09 (-7.07 to -1.11)*	*0.009*	
Problems with social eating		*-0.20 (-0.40 to 0.00)*	*0.050*	

Table 10.32: Coefficients and P values for variables independently associated with baseline global QoL in HN patients.

10.3.9 T3: QoL at one month post treatment

10.3.9.1 CR model (T3 QoL)

HADS-D was the only variable independently associated with poorer global QoL at T3 in CR patients

Univariate associations (N)
CT (20)
NE (21)
HADS-D (25)
T3 EORTC-QLQ symptoms:
Body image (9)
Fatigue (25)
Micturition problems (9)
Appetite loss (25)
Health anxiety (15)
Dyspnoea (24)
Constipation (25)
HADS-A (52)
Increasing age (25)

Table 10.33: Univariate associations between variables and global QoL at T3 in CR cancer patients. EORTC-QLQ symptoms are given in order of R^2.

- Table 10.33 shows the variables that are univariately associated with poorer QoL at T3 in CR cancer patients.
- Too few people completed the body image, micturition problems and health anxiety scales for these items to be used in the multivariate models.
- After entering HADS-D into the model, HADS-D was found to be the only significant independent variable associated with poorer QoL at T3.
- Including T stage, N stage, age comorbid disabilities, sex, chemotherapy, baseline QoL, HADS-D or using bootstrapped standard errors all made no difference to the model and the same model was derived when using a stepwise approach.

Variable	N	ß (CI)	P value	Adjusted R^2
HADS-D	*25*	*-4.25 (-6.58 to -1.92)*	*0.001*	*0.75*

Table 10.34: Coefficients and P values for variables independently associated with T3 global QoL in CR patients.

10.3.9.2 HN model (T3 QoL)

HADS-D, smoking and dry mouth were the only significant independently associated variables (see table 10.36). Univariate associations are presented in table 10.35.

Univariate associations (N)
PH depression
LE (44)
HADS-D (45)
T2 IL6 and CRP (37,37)
Perioperative IL6 and CRP (36, 35)
T3 TNFα
T3 EORTC-QLQ symptoms:
Fatigue (45),
Dry mouth (31)
Pain (45)
Speech problems (30)
Insomnia (45)
Financial difficulties (44)
Senses problems (31)
Constipation (45)
Problems with social eating (30)
Sticky saliva (31)
Problems with social contact (30)
Nausea and vomiting (45)
On feeding tube (30)
Diarrhoea (44)
Less sexuality (24)
Dyspnoea (44)
Nutritional supplements (30)
Pain killers (30)
Swallowing (31)
Coughing (31)
HADS-A (45)
Alcohol abuse (42)

Table 10.35: Univariate associations between variables and global QoL at T3 in HN cancer patients. EORTC-QLQ symptoms are given in order of R^2.

- PH depression, LE, and alcohol abuse were no longer significant after adjusting for HADS-D.
- None of the inflammatory factors were significant after adjusting for T2 IL6, but this was no longer significant after adjusting for smoking.
- Comorbid disability confounded HADS-D and chemotherapy confounded dry mouth and smoking.
- Dry mouth was also confounded by surgical rating, T1 HADS-D and global QoL, but no other variables affected the model.
- All the variables in the model were still significant when using bootstrapped errors. The model is the same as the one obtained when using a stepwise approach.
- Univariate analyses showed no biases in the complete case sample, except some indication of a reduced relationship between dyspnoea and QoL in the analysed sample.

Variable	N	ß (CI)	P value	Adjusted R^2
Fatigue	*27*	*-0.37 (-0.57 to -0.17)*	*0.001*	*0.77*
HADS-D		*-2.02 (-3.59 to -0.45)*	*0.014*	
Dry mouth		*-0.16 (-0.30 to -0.02)*	*0.025*	
Current smoker		*-10.49 (-19.53 to -1.46)*	*0.025*	

Table 10.36: coefficients and p values for variables associated with global QoL at T3 in HN patients.

10.3.10 T4: QoL at three months post treatment

10.3.10.1 CR model (T4 QoL)

Only comorbid disability and LE were significantly independently associated with poorer QoL in CR patients (see table 10.38).

Univariate associations (N)
CT (19)
NE(21)
LE (21)
HADS-D (24)
T4 EORTC-QLQ symptoms:
Loss of libido (m 7, f 4),
Impotence (5),
Health anxiety (17),
Dyspnoea (23),
Abdominal/pelvic pain (12)
Current smoking (19)
Comorbid disability (24)

Table 10.37: Univariate associations between variables and global QoL at T4 in CR cancer patients. EORTC-QLQ symptoms are given in order of R^2. m=male, f=female.

- Table 10.37 shows the variables univariately associated with global QoL at T4.
- Loss of libido, impotence, health anxiety and abdominal/pelvic pain were not included in multivariate analyses due to low numbers.
- LE, NE and CT were no longer significant after adjusting for HADS-D.
- Comorbid disability explained more of the variance than HADS-D in which case LE could be re-entered into the model. No other symptoms were significant.
- T stage and age confounded LE, but no other variables from the core set affected the model.
- All of the variables were still significant when using bootstrapped standard errors and using a stepwise approach reached the same model.
- Post hoc univariate analyses showed no biases in the complete case sample.

Variable	N	ß (CI)	P value	Adjusted R^2
Comorbid disability	*24*	*-17.26 (-26.82 to -7.69)*	*0.001*	*0.45*
LE		*-4.65 (-8.82 to -0.48)*	*0.030*	

Table 10.38: Variables associated with T4 global QoL in CR patients.

10.3.10.2 HN model (T4 QoL)

The final model included fatigue, current alcohol consumption and LE (see table 10.40).

Univariate associations (N)
NE(41)
PH depression
LE (39)
HADS-D (41
Trend CT (34))
T4 EORTC-QLQ symptoms:
Fatigue (41)
Pain (41)
Problems with senses (32)
Problems with speech (29)
Problems with social contact (29)
Dyspnoea (41)
Less sexuality (27)
Appetite loss (41)
Financial difficulties (41)
Insomnia (41)
HADS-A (41),
T stage (40)
Current alcohol consumption (37).

Table 10.39: Univariate associations between variables and global QoL at T4 in HN cancer patients. EORTC-QLQ symptoms are given in order of R^2.

- Table 10.39 shows the variables univariately associated with poorer QoL at T4.
- Neuroticism, PH depression and HADS-A were no longer significant after adjusting for HADS-D.
- HADS-D was no longer significant after adjusting for fatigue.
- None of the core set of variables were significant or confounded the results, nor did baseline HADS-D or global QoL.
- All of the results were still significant when using bootstrapped standard errors and using a stepwise approach came to the same conclusion.
- Post hoc univariate analyses showed no biases in the complete case sample.

Variable	N	ß (CI)	P value	AdjustedR^2
Fatigue	*35*	*-0.41 (-0.54 to -0.27)*	*<0.0005*	*0.57*
*Current alcohol use**		*-15.00 (-23.77 to -6.44)*	*0.001*	
LE		*-4.86 (-7.65 to -2.06)*	*0.001*	

Table 10.40: Variables associated with poorer global QoL at T4 in HN patients. * N=30 vs 7.

10.3.11 T5: QoL at six months post treatment

10.3.11.1 CR model (T5 QoL)

Only HADS-D and comorbid disability were significantly independently associated with poorer QoL at T5 (see table 10.42).

Univariate associations (N)
CT (17)
HADS-D (24)
T5 EORTC-QLQ symptoms:
Dry mouth (19)
Fatigue (21)
Body image (14)
Hair loss (19)
Comorbid disability (21)

Table 10.41: Univariate associations between variables and global QoL at T5 in CR cancer patients. EORTC-QLQ symptoms are given in order of R^2.

- Table 10.41 shows the variables univariately associated with poorer global QoL at T5
- Dry mouth, body image and hair loss were not included in the multivariate analyses because very few patients completed the body image scale and less than 2 patients reported any symptoms for the other excluded scales.
- Childhood trauma and fatigue were no longer significant after adjusting for HADS-D.
- Baseline global QoL and age, both confounded the effect of comorbid disability.
- Using bootstrapped standard errors did not affect the model and the same model was derived when using a stepwise approach.
- Post hoc univariate analyses showed no biases in the complete case sample.

Variable	N	ß (CI)	P value	Adjusted R^2
HADS-D	*21*	*-4.82 (-6.76 to -2.89)*	*<0.0005*	*0.61*
Comorbs		*-13.85 (-23.39 to -4.30)*	*0.007*	

Table 10.42: Variables associated with poorer global QoL at T5 in CR patients.

10.3.11.2 HN model (T5 QoL)

Fatigue and dyspnoea were the only variables significantly independently associated with poorer QoL at T5 in HN patients (see table 10.44).

Univariate associations (N)
HADS-D (40)
T1 IFNγ (36)
T2 IL6 (40)
T5 EORTC-QLQ symptoms:
Fatigue (40),
Dyspnoea (40),
Constipation (40),
Less sexuality (35),
Speech problems (38),
Problems with social contact (38),
Pain (40),
Problems with teeth (36),
Problems with social eating (38),
Coughing (39)
Restricted mouth opening (39)

Table 10.43: Univariate associations between variables and global QoL at T5 in HN cancer patients. EORTC-QLQ symptoms are given in order of R^2.

- Table 10.50 shows variables univariately associated with QoL at T5.
- IFNγ was no longer significant after adjusting for IL6.
- HADS-D and IL6 were both independently associated with poorer QoL when adjusting for each other, but neither was significant after adjusting for fatigue and dyspnoea.

- Dyspnoea was confounded by surgical rating, otherwise none of the core set of variables affected the model or were significant.
- Baseline HADS-D was not significant and did not affect the model. Baseline global QoL did not confound or mediate the other variables, but was significantly associated with QoL at T5.
- Using a stepwise approach generated the same model and using bootstrapping methods did not change the model.
- Post hoc univariate analyses showed no biases in the complete case sample.

Variable	N	ß (CI)	P value	Adjusted R^2
Fatigue	*40*	*-0.35 (-0.55 to -0.40)*	*0.001*	*0.44*
Dyspnoea		*-0.33 (-0.58 to -0.07)*	*0.013*	

Table 10.44: Variables associated with poorer global QoL at T5 in HN patients.

10.3.12 Longitudinal analyses: QoL at all time points

10.3.12.1 CR model (overall QoL)

The final model included HADS-D, fatigue and past smoking as the only variables significantly associated with poorer QoL (see table 10.46).

Univariate associations (N)
CT (20)
NE (22)
PH depression
HADS-D (34)
Overall EORTC-QLQ symptoms:
Fatigue (34)
Dry mouth (26)
Loss of libido (m 8)
Impotence (7)
Nausea and vomiting (34)
Appetite loss (34)
Constipation (34)
Insomnia (34)
Dyspnoea (34)
Problems with taste (26)
Age (34)
Comorbid disability (33)
HADS-A (34)
Past smoking (25)

Table 10.45: Univariate associations between variables and overall global QoL in CR cancer patients. EORTC-QLQ symptoms are given in order of R^2. m=male.

- Table 10.45 shows the variables univariately associated with overall QoL.
- Life events were no longer significant after adjusting for CT.
- Neuroticism was no longer significant after adjusting for CT.
- Fatigue confounded CT.
- Smoking was partially mediated by comorbidity and surgical rating, but none of the other demographic or cancer related variables affected the model.

- All of the variables in the model were still significant after bootstrapping and was the same as the stepwise derived model
- Univariate post-hoc analyses indicated no biases in the complete case sample.

Variable	N	ß (CI)	P value	Between R^2
HADS-D	*25*	*-3.01 (-4.33 to -1.76)*	*<0.0005*	*0.76*
Fatigue		*-0.43 (-0.65 to -0.22)*	*<0.0005*	
Past smoking		*-9.21 (-18.34 to -0.08)*	*0.048*	

Table 10.46: Variables associated with poorer QoL in CR patients.

10.3.12.2 HN model (overall QoL)

HADS-D, fatigue, financial difficulties, current alcohol consumption and nausea and vomiting were the only variables significantly independently associated with poorer QoL at T5 in HN patients (see table 10.48).

Univariate associations (N)
PH depression
LE (45)
HADS-D (56)
Overall EORTC-QLQ symptoms:
Fatigue (56)
Dyspnoea (56)
Nausea and vomiting (56)
Constipation (56)
Problems with social contact (51)
Insomnia (56)
Financial difficulties (56)
Problems with social eating (51)
Speech problems (51)
Less sexuality (49)
Nutritional supplements (51)
Use of feeding tube (51)
Weight loss (51)
Appetite loss (56)
Diarrhoea (56)
Problems with senses (51)
Sticky saliva (51)
Coughing (51)
Dry mouth (50)
Pain killers (51)
T stage (55),
HADS-A (56)
Current alcohol consumption (45)

Table 10.47: Univariate associations between variables and overall global QoL in HN cancer patients. EORTC-QLQ symptoms are given in order of R^2. m=male.

- Table 10.47 shows the variables univariately associated with overall QoL in HN cancer patients.
- Neuroticism and PH of depression were no longer significant after adjusting for HADS-D.
- Life events were no longer significant after adjusting for fatigue.
- Nausea and vomiting was slightly confounded by surgical rating, but adjusting for any other variables in the core set did not affect the model.
- The same model was derived when using a stepwise approach and using bootstrapped standard errors did not affect the model.
- Univariate post-hoc analyses indicated no biases in the complete case sample.

Variable	N	ß (CI)	P value	Between R^2
Fatigue	*45*	*-0.30 (-0.42 to -0.18)*	*<0.0005*	*0.53*
HADS-D		*-1.56 (-2.71 to -0.41)*	*0.008*	
Financial difficulties		*-0.08 (-0.15 to -0.02)*	*0.014*	
Alcohol consumption		*-8.64 (-15.30 to -1.98)*	*0.011*	
Nausea/vomiting		*-0.16 (-0.30 to -0.02)*	*0.026*	

Table 10.48: Variables associated with poorer QoL in HN patients.

10.4 Summary

Time	HADS-D	QoL
T1	Fatigue Sex	HADS-D Fatigue T stage
T3	Neuroticism Baseline TNFα	HADS-D
T4	Childhood trauma Fatigue Neuroticism Financial difficulties	Comorbid disability Life events
T5	Diarrhoea Childhood trauma	HADS-D Comorbid disability
Longitudinal	Life events Neuroticism Constipation Fatigue	HADS-D Fatigue Past smoking

Table 10.49: Variables associated with increased HADS-D and poorer QoL in CR cancer patients

Time	HADS-D	QoL
T1	Fatigue Neuroticism	Fatigue Nausea and vomiting T stage Problems with social eating
T3	Life events Constipation Pain Lack of weight gain	Fatigue HADS-D Dry mouth Current smoking
T4	Problems with social contact Neuroticism	Fatigue Current alcohol use Life events
T5	Fatigue Less sexuality Childhood trauma	Fatigue Dyspnoea
Longitudinal	Fatigue Less sexuality Diarrhoea Neuroticism	Fatigue HADS_D Alcohol consumption Financial difficulties Nausea and vomiting

Table 10.50: Variables associated with increased HADS-D and poorer QoL in HN cancer patients

10.5 Discussion

Table 10.49 and table 10.50 show the variables associated with increased depressive symptoms and poorer QoL at each time point and overall in CR cancer patients and HN cancer patients respectively.

This discussion addresses each time point in turn, followed by a comparison of time points. The variables associated with depressive symptoms are compared to those associated with a DE6. Each section first summarises findings for HADS-D for CR and HN cancer patients, interpreting the findings and comparing the results of the two cancer groups. This is followed by a similar structure for the QoL findings. Finally, the HADS-D and QoL findings are interpreted together. The discussion concludes with a summary of the main theme of the results referring to the hypotheses and a review of the overall strengths and weaknesses.

10.5.1 Baseline findings

Fatigue and sex (female) were the only variables independently associated with increased depressive symptoms at baseline in CR cancer patients. These variables explained 40% of the variance in depressive symptoms. Similarly, only fatigue and NE were independently associated with increased depressive symptoms in HN cancer patients, explaining 47% of the variance in HN patients' baseline HADS-D scores. The results were not explained by any other demographic or cancer related factor. Fatigue is highly associated with depression and is one of the symptoms of a DD[343], thus levels of fatigue are likely to be associated with depressive symptoms. Neuroticism and sex are also likely to be associated with increased depressive symptoms: past studies have reported strong associations between NE and depression (see McWilliams, 2003[344]) and women in the general population have been found to report higher depressive symptoms[345]. Women are also at 1.5x greater odds of developing a DD[59]. Women are also more likely to show high levels of NE compared to men[337], suggesting some similarity between the CR and HN model. Thus, the variables associated with depressive symptoms at baseline in both CR and HN cancer

patients are factors related to depression and similar to what would be expected in the general population.

Baseline TNFα levels were associated with poorer baseline QoL in CR patients. However, this relationship was no longer significant after adjusting for T stage. After including extent of tumour (T stage) in the model, only T stage, depressive symptoms and fatigue were independently associated with poorer QoL, explaining 70% of the variance of QoL scores. Whereas in HN patients, T stage, fatigue, nausea and vomiting and problems with social eating were all associated with poorer QoL at baseline, explaining 75% of the variance of HN patient QoL scores. Interestingly, as reported in chapter 9, TNFα was also highly related to fatigue. This suggests that T stage is associated with higher TNFα levels, thus increased T stage may be associated with poorer QoL partially due to increased TNFα production and fatigue. However T stage is probably also related to other aspects of function, thus has a greater association with poorer QoL, compared to TNFα levels alone. Self-reported somatic symptoms in HN cancer patients appear to have a large impact on their global QoL at baseline, more so than depressive symptoms. Whereas depressive symptoms were strongly related to QoL in CR cancer patients, even in the multivariate analysis. This may be because HN patients have a higher cancer related symptom burden than CR cancer patients before treatment. However, it is important to note that fewer CR cancer patients completed the cancer specific aspects of the QoL questionnaire, therefore, due to low numbers, cancer specific symptoms are less likely to be included in the CR cancer models.

No cancer related factors were associated with depressive symptoms at baseline in CR or HN cancer patients. On the other hand, T stage was associated with poorer QoL in both groups of cancer patients. Also, whilst the factors associated with depressive symptoms were similar in CR and HN cancer patients, the variables associated with poorer QoL appeared to be more symptom related in the HN group than in the CR group.

10.5.2 T3: One month post treatment

Increased baseline TNFα levels and NE were the only variables associated with increased depressive symptoms at T3 in CR cancer patients, explaining 76% of the variance in HADS-D scores. Life events, pain and constipation were the only variables associated with increased depressive symptoms at T3 in HN cancer patients, and weight gain was associated with decreased depressive symptoms. In total LE, pain, constipation and weight gain explained 77% of the variance in HADS-D scores for HN cancer patients. This shows that the association between baseline TNFα and increased depressive symptoms at one month post surgery in CR cancer patients is a robust finding as it has a higher impact than any other cancer related of psychological factor. Also, the association between TNFα levels and depressive symptoms remains after adjustment for baseline global QoL. No association between inflammation and HADS-D was found in univariate analyses as reported in chapter 8 on the role of physiological factors. However, a similar amount of variance of depressive symptoms in HN cancer patients, compared to the amount explained in CR patients, has been explained through somatic symptoms and stressful LE. Thus, inflammation is an important risk factor for increased depressive symptoms one month after surgery in CR cancer patients, but LE and current symptoms are more important factors in HN cancer patients.

Depressive symptoms was the only variable independently associated with poorer QoL one month post treatment in CR cancer patients, which explained 36% of the variance in QoL scores alone. Whereas, HADS-D, fatigue, dry mouth and current smoking were the only variables independently associated with poorer QoL in HN cancer patients, collectively explaining 77% of the variance. The CR cancer finding demonstrates the strength of the relationship between HADS-D and global QoL in CR cancer patients. However, once again, somatic symptoms appear to play a more important role in HN cancer patients. It is interesting that current smoking is related to poorer QoL at this time point in HN cancer patients. This may be because the smokers are struggling to break their addiction. Also, a recent study found an association between current smoking and increased pain in HN patients before treatment[346]. Dry mouth may be a particular problem in HN cancer

patients that have started chemoradiation treatment. Part of the association between dry mouth and QoL was related to chemotherapy, as indicated by the mediating effect of chemotherapy. Symptoms of dry mouth in HN cancer patients have been shown to start within two months after primary treatment in samples where a large proportion of patients were undergoing radiotherapy treatment[146, 347]. Moreover, these symptoms endured over the next year, with only a slight reduction by five years post treatment[146, 347, 348]. Nevertheless whilst the symptoms of dry mouth persisted, patients' global QoL improved[124, 347], suggesting that the association between dry mouth and poorer global QoL decreases over time. This is supported by the finding that dry mouth is associated with poorer global QoL in HN cancer patients at T3, but not at any later time points. Thus, depressive symptoms are the only factor associated with poorer QoL in CR cancer patients. Depressive symptoms are strongly associated with poorer QoL in HN cancer patients, but fatigue, dry mouth and smoking are also independently related to poorer QoL.

It is noteworthy that increased inflammation was a risk factor for increased depressive symptoms one month after surgery in CR cancer patients and this relationship was not affected by any cancer related variables. Inflammation was not associated with increased depressive symptoms in HN patients. As stated in chapter 9, this could be due to the greater heterogeneity of the HN cancer group. In both the HN and CR cancer patients the models explained a lot of the variance in HADS-D scores. Depressive symptoms were independently related to poorer QoL in both cancer groups, indicating the importance of depressive symptoms in cancer patient treatment outcome at one month after surgery.

10.5.3 T4: Three months post treatment

Childhood trauma, fatigue, NE and financial difficulties were the only variables independently associated with depressive symptoms in CR cancer patients, explaining 71% of the variance. Neuroticism and problems with social contact were the only variables associated with increased depressive symptoms in HN cancer patients, explaining 52% of the variance. Similarly, T3 somatic symptoms

appear to be more important factors in HN cancer patients than CR cancer patients. The results for this time point for the HN cancer patients are similar to the findings from the cross sectional study reported in chapter 4. The cross sectional analyses found fatigue and problems with social contact were associated with increased depressive symptoms in HN cancer patients. As reported in chapter 9, NE was also associated with increased fatigue post treatment, thus the two variables are strongly related and NE may have been an important factor in the cross sectional analyses had the information been available. The variables associated with HADS-D in CR patients were markedly different to those in the cross sectional study, which were fatigue, body image and defaecation problems. However, this could be due to the low completion rates for cancer specific symptoms in the CR group.

Life events and comorbid disability were the only variables that were associated with poorer QoL in CR cancer patients at three months post treatment, explaining 45% of the variance. Fatigue, alcohol consumption and LE were the only variables associated with poorer QoL in CR cancer patients, explaining 57% of the variance. It is intriguing that despite the high level of variance explained by HADS-D at one month post treatment, at this time point HADS-D was not independently associated with QoL in either cancer group. However, LE as reported in chapter 7, were strongly associated with increased depressive symptoms. Also, as reported in chapter 9, LE were strongly related to increased fatigue and increased pain at this time point in CR patients. This suggests that LE may be an important factor influencing both increased depressive symptoms and poorer QoL in post operative ambulatory cancer patients.

The adjusted models for T4 explain less of the variance of depressive symptoms and QoL than those of T3, but still explain at least 40% of the variance. Similar to the findings at T3, somatic symptoms are related to increased depressive symptoms in HN cancer patients, but not CR cancer patients. This may be due to the low completion rates in the CR cancer sample. Notably, depressive symptoms were not independently associated with poorer QoL in either cancer group, whereas LE appeared to be more influential factors. Previous studies have also

found that LE are strongly related to depressive symptoms: LE, NE and ethnicity accounted for 53% of the variance in depressive symptoms in breast cancer patients three months post surgical treatment[210]. In addition, 88% of the variance in depressive symptoms in a sample of breast cancer patients three months past treatment was explained by number of stressful LE and PH of depression[349]. This study shows that the number of stressful LE a patient experiences around the time of the cancer diagnosis is also an important risk factor for poorer QoL three months post treatment.

10.5.4 T5: Six months post treatment

Only CT and diarrhoea were independently associated with increased depressive symptoms at T5 in CR cancer patients, explaining 56% of the variance in HADS-D scores. Furthermore, only CT, fatigue and less sexuality were associated with increased depressive symptoms in HN cancer patients, explaining 60% of the variance in HADS-D scores. The CR findings for this time point indicate some association between cancer specific symptoms and increased depressive symptoms. This is especially true when compared to the findings from the cross sectional study showing defaecation problems to be one of the variables with the strongest association with depressive symptoms. Similarly, less sexuality (less desire and enjoyment) was significantly associated with increased depressive symptoms in HN cancer patients, which has been reported as an important factor in HN cancer patients post treatment[350]. It is interesting that CT was a significant factor in both cancer groups, and it remains an important risk factor for high depressive symptoms in cancer patients, even when adjusting for symptoms.

Only HADS-D and comorbid disability were independently associated with poorer QoL in CR cancer patients, explaining 61% of the variance. Whereas only fatigue and dyspnoea were associated with poorer QoL in HN cancer patients, explaining just 44% of the variance. The factors most associated with poorer QoL in the cross sectional study were HADS-D, taste problems, dry mouth and sore skin. Given the low completion rate of the symptom aspects of the CR specific questionnaire in the prospective study, these results may be comparable. Similarly, the variables most

associated with poorer QoL in HN cancer patients in the cross sectional study were fatigue, problems with social contact, age and pain: indicating that fatigue is an important issue in HN cancer patients, whereas depressive symptoms are an important factor in CR cancer patients.

10.5.5 Overall

In the longitudinal analyses only fatigue, NE, LE and constipation were associated with HADS-D in CR cancer patients, explaining 79% of the variance. Fatigue, NE, less sexuality and diarrhoea were the only variables significantly associated with depressive symptoms in HN cancer patients, explaining 56% of the variance. This shows that fatigue is consistently associated with depressive symptoms over time in both cancer groups, which would be expected given the close association between fatigue and depression. Similarly, NE is strongly associated with depressive symptoms in both patient groups, again this would be expected given the close relationship between NE and depressive symptomatology (see McWilliams, 2003[344]).

Only HADS-D, fatigue and past smoking were independently associated with poorer QoL overall in CR cancer patients, explaining 76% of the variance. Interestingly fatigue, HADS-D, alcohol consumption, financial difficulties and nausea and vomiting were the only variables independently associated with poorer QoL in HN cancer patients, explaining 53% of the variance. This is interesting because only depressive symptoms were related to poorer QoL at T3 in the previous analyses. This, perhaps, indicates that HADS-D is consistently associated with poorer QoL, but there is only a small effect. A similar effect could explain the finding of financial difficulties and nausea and vomiting. Furthermore, the association between past smoking and poorer QoL in CR cancer patients may be due to a similar effect and is perhaps related to comorbid disability; smoking is a risk factor for many chronic diseases, such as stroke, heart attack or emphysema. Current smoking was unlikely to be significant as only three people in the CR group smoked at the time of the study. Despite past studies suggesting an important role for body image in CR cancer patients[57, 174], body image was not significant in any

of the multivariate models. However, it was often associated with depressive symptoms in CR cancer patients, but not included in the final models due to low numbers.

Overall, there does not appear to be a clearly discernable pattern between the investigated psychological and physiological variables, EORTC-QLQ symptoms and depressive symptoms in either the CR or HN cancer group. This is probably partly explained by the close inter-relationships between the investigated variables and symptom reporting. Also, large fluctuations in patient well-being, in terms of their level of symptoms and mood, could occur soon after treatment, which would also be affected by their cancer type and treatment regime. These issues could obscure any patterns, which is possible given the low power.

One notable pattern is that the hypothesised psychological and physiological variables appear to be more relevant to depressive symptoms than to global QoL. However, depressive symptoms are often related to QoL, suggesting that depressive symptoms may be on a pathway from predisposition to depression to poorer QoL post treatment. This could only be investigated using structural equation modelling which would require much larger samples. Also, it is interesting that variables that were not significant when analysed at each time point were significant in the longitudinal analyses. This indicates that they may have a small but consistent effect. Given the fluctuations in these associations over this period of time, longitudinal analyses may not be the most appropriate form of analysis, but they can indicate which are the most robust aetiological factors overall.

When combined with the cross sectional results, depressive symptoms appear to be strongly related to poorer QoL in CR cancer patients, but less so in HN cancer patients. Although past studies have found associations between increased depressive symptoms and poorer QoL in HN cancer patients[56], these results had not been adjusted for other factors. Depressive symptoms are associated with poorer QoL in HN cancer patients in both the cross sectional and prospective studies, but after adjustment fatigue appears to have a stronger association with poorer QoL. Also, some factors, such as dry mouth in HN cancer patients are

related to poorer QoL at one month post operation, but then not from then on. Although the symptoms of dry mouth persist for over a year, overall QoL is reported to return to near baseline levels by 12 months[56]. This could be because patients adjust to the symptoms.

10.5.6 Depressive disorder compared to depressive symptoms

Past history of depression, NE and LE were associated with increased likelihood of a DE6, explaining 59% of the variance. As no symptoms were associated with increased risk of depression, a longitudinal analysis was carried out in order to give fair representation of the symptoms. However, even in these analyses only PH depression, NE, LE and surgeons' rating of extent of surgery and complications were related to an increased risk of a DE6. Notably, whilst somatic and cancer related symptoms were associated with increased depressive symptoms, they were not associated with increased risk of a DE6. This could be because depressive symptoms are a common response to cancer diagnosis and treatment, but only those individuals who have an underlying vulnerability to stressors are at increased risk of a DE. However, whilst depressive symptoms were associated with poorer QoL a DE was not. This could be an effect of the study design because DE6 was only coded as 'present' or 'absent' whereas symptoms and QoL varied at each time point. When compared to the cross sectional results for CR patients, although HADS-D and PH depression were the most significant factors associated with a DE, body image was also significantly associated with increased risk of a DE. In agreement with past studies, the symptoms that impact on function were strongly associated with increased depressive symptoms[123, 177]. No other studies have investigated baseline psychological factors compared to symptoms with respect to risk of a DE in either CR or HN cancer patients, therefore it is worth investigating the relationship of psychological variables further.

10.5.7 Limitations and conclusions

The study is limited by low power, which may have led to some inconsistent findings. Also, the relatively small numbers mean that although the models have high explanatory power in these samples, the models are unlikely to fit so well in

other samples. As reported in section 6.2, there is also a bias towards healthier individuals taking part in the study, which may have affected the results. Due to the low numbers of patients that experienced a DE6, it was not possible to code DE according to time, which may have obscured any associations with symptoms or global QoL.

It is acknowledged that in order to reach the final models many tests were carried out. This was necessary to determine which factors are most strongly associated with increased depressive symptoms and poorer QoL at each time point. However, this was carried out in an exploratory manner thus the results are reported in such a way as to identify trends to inform future studies. Also, very little research had previously compared the comparative associations between psychological and cancer related risk factors for depression in curative cancer patients.

Whilst it is important to gain insight into how perceived symptoms are associated with poorer QoL, it would be really interesting to investigate how the investigated factors relate to cancer related symptoms, depressive symptoms and poorer QoL. This could only be investigated using much larger samples and structural equation modelling, which could show the direct and indirect pathways to poorer QoL. Furthermore, some variables that could be considerable covariates are not included in this study. For instance, it is beyond the scope of this thesis to include analyses and adjustments for the many well founded genetic influences on inflammation, depression and QoL. Future studies with larger samples should also consider measuring social economic status, which has been found to be associated with increased depressive symptoms[66], though the analyses were not adjusted for relevant social variables such as smoking. Nonetheless, social economic status has also been inversely associated with increased IL6 and CRP levels. Although the association between greater social economic status and decreased CRP levels was no longer significant after adjustment for lifestyle factors, the association between IL6 and community social economic status remained even after adjusting for lifestyle factors, personal income and education[351]. Medication is also likely to affect inflammatory levels, but due to the

small number of participants and large number of medications it is impractical to adjust for each medication.

Based on past studies it was expected that cancer related variables would have limited effect[214]. The results from this study show that the clinical measures of cancer, such as extent of tumour and treatment mode, have relatively little impact on depressive symptoms or QoL. They also show that symptoms associated with cancer are related to depressive symptoms and QoL, but not a DE6. The results indicate that depressive symptoms and global QoL in cancer patients soon after treatment are related to both established vulnerability factors common to individuals in the general population and to current symptoms due to the cancer. However, as reported in chapter 9, patients' perceived symptoms were also affected by factors considered to increase the risk of a DE. Using both vulnerability and symptom measures resulted in models which explained a high proportion of the variance in depressive symptoms and QoL scores in CR and HN cancer patients.

This study also found an association between TNFα and prospective depressive symptoms in CR cancer patients. Previous studies have found cross sectional associations between increased inflammation in cancer patients with a DD compared to cancer patients without a DD[138-140]. Inflammation has been shown to be positively associated with depressive symptoms in cancer patients[141]. This is the first study to look at a prospective association and to use multivariate measures to adjust for other factors that may confound the relationship between inflammation and depression. This indicates the importance of psychological and physiological risk factors for depression in cancer patients alongside cancer related issues in respect to cancer patients self rated QoL.

This chapter further tested the study hypotheses (section 2.7.1) by exploring how cancer related factors mediate the relationship between the investigated variables and depressive symptoms and QoL in cancer patients. Patients with a PH depression were at increased risk of a DE6 and this relationship remained even after adjusting for cancer related factors. The association between increased

cytokine levels and increased depressive symptoms in CR cancer patients was stronger then that of any other cancer related variables. Finally, depressive symptoms have a stronger association with QoL in CR cancer patients than any other variable, but this is not true for HN cancer patients.

In summary, this chapter combined the results from the previous three chapters on psychological and physiological risk factors for depression in cancer patients addressing the third aim of the study: to explore associations between other possible explanatory factors and depressive symptoms and poorer QoL in cancer patients. As there was a lot of covariance between many of the investigated variables, using multivariate analyses helped to identify which variables would be most predictive of later depressive symptoms and QoL, and therefore which would be most clinically useful. Whilst some of the results may appear quite random, some patterns did emerge:

1. There was a close relationship between inflammation and mood in CR cancer patients though this was not as apparent in the HN cancer group.
2. Cancer related symptoms had a stronger association with depressive symptoms and poorer QoL in HN cancer patients compared to CR cancer patients.
3. HADS-D was strongly related to QoL in both patient groups, but more so in the CR cancer group. Whereas fatigue appeared to be a more important factor with respect to HN cancer patients' self rated global QoL.

This chapter addressed the third exploratory aim of the thesis and has reported the relative importance of CT, NE, LE, PH of depression and increased inflammation as markers of increased depressive symptoms, poorer QoL and increased risk of a DE in patients soon after a diagnosis of cancer.

A summary and discussion of the clinical implications of the data from this chapter and the previous sections are presented in the next and final chapter.

PART IV

General discussion

11 General discussion

This section discusses the overall conclusions that can be drawn from the results of this study. Firstly, a summary of the data from each section and how these relate to the original aims of the thesis are presented. This is followed by a discussion of the clinical significance of these findings, with reference to cancer patient treatment, as well as the research implications of the study. The methods of the prospective study are critically discussed with suggestions for possible improvements. Finally, the practical applications and recommendations are reported.

11.1 Aims and findings

The main aims of this study were to:

3. Measure the prevalence of depressive disorders in two different cancer clinic populations (at Barts and The London).
4. Test the hypotheses that:
    (i) Patients with a PH of depression are more likely to experience a DE following a cancer diagnosis.
    (ii) Depressive symptoms have a significant negative effect on QoL.
    (iii) Patients with higher cytokine levels show more depressive symptoms.
    (iv) Patients with increased HPAA activity (increased salivary cortisol levels) will show increased depressive symptoms.
    (v) Patients with increased HPAA activity will show increased inflammation (increased cytokine and CRP levels).
5. Explore associations between other possible explanatory factors on depressive symptomatology, inflammation and cortisol dysregulation, such as associations between coping styles, personality and patient rated cancer related symptoms and depressive symptoms.

The cross sectional study (chapter 4) addressed Aim 1 and showed an estimated point prevalence of a DD of 14% in CR cancer patients and 5% in HN cancer patients. The study also tested the first two hypotheses and found that patients with a PH depression were more likely to experience a DE following a cancer diagnosis and depressive symptoms were associated with poorer QoL. These findings were further supported by work from the prospective study, which found a six month prevalence of DD of 12% in CR cancer patients and 21% in HN cancer patients (chapter 6). Again, there was a significant negative association between depressive symptoms and poorer QoL.

Chapter 7, on the role of psychological factors, supported the findings from the cross sectional study, showing that patients with a PH depression are at increased risk of a DE6 and have higher levels of depressive symptoms. Chapter 7 also explored the effect of mediating factors on depressive symptomatology and QoL. The results showed that LE and NE significantly increased the probability of a DE6. Childhood Trauma, PH depression, LE and NE were each associated with increased depressive symptoms and poorer QoL. However, there was little consistent effect of coping style. Chapter 8 investigated the role of physiological factors in depressive symptoms and QoL, addressing hypotheses iii and iv. Very few reliable associations between cortisol and depression or QoL measures were found, but there was evidence of a prospective association between increased inflammation and later increased depressive symptoms in CR cancer patients: increased levels of the pro-inflammatory cytokine TNFα were associated with increased depressive symptoms at later time points.

Chapters 9 and 10 addressed hypothesis v and aim 3. Chapter 9 reported on the inter-relations of the investigated variables and the association between the investigated variables and some of the self report symptoms on the EORTC-QLQ (fatigue and pain) providing evidence of an association between CT and increased inflammation. Besides CT, there were no associations between inflammation and any other psychological variables, or between cortisol and any psychological variables. There were also no associations between cortisol levels and increased inflammation, counter to the hypothesis. However, many of the psychological and inflammatory measures were associated with increased fatigue and pain.

Finally, chapter 10 reported on the factors most strongly associated with increased depressive symptomatology and poorer QoL, addressing the third aim of the thesis. Psychological factors such as NE, LE and CT were important risk markers for increased depressive symptoms and poorer QoL in both CR and HN cancer patients. Inflammation was also associated with increased depressive symptoms post surgery in CR cancer patients. Current patient-reported symptoms were also

important factors in predicting later depressive symptoms and poorer QoL, but objective cancer related factors were less likely to be significant in the multivariate models.

11.2 Clinical significance

11.2.1 Treatment outcome

The reported results and previous discussions focus on statistical significance, but statistically significant associations and differences do not necessarily translate to clinically significant relationships. Large samples can result in statistically significant findings from a relatively small change in QoL scores that would not make much difference clinically. One of the advantages of examining a small sample is that the lower power requires a bigger change for statistical significance, thus more likely to have clinical significance. However, this is with the proviso that the sample is representative and can be generalised to patient populations. In terms of the clinical significance of the EORTC-QLQ, some researchers suggest a change greater than the standard error mean of the results indicates a significant change as it indicates a change greater than that due to chance[352, 353]. In this sample, that would mean that a change of more than three points on the global QoL scale would be clinically significant, whereas, others have suggested that a 10 point change on the EORTC-QLQ indicates clinical significance. This is especially important given the scoring translation procedure of the EORTC-QLQ, which scales every score from 0-100. Therefore, with respect to the global QoL measure, the minimal change is seven points (based on the transformation of two seven item scales). This implies that a patient increasing or decreasing their response on the Likert scale by just one point is clinically significant.

To give an example: for every one point on the HADS, a patients' QoL decreases by between three and four points, which may indeed indicate a significant change – depending on which definition of clinical significance is chosen. Additionally, for every one pg/ml increase in baseline TNFα, a patient's HADS-D score at one

month post operation increases by one (the HADS-D range is 0-21). Given the range of baseline TNFα levels in CR patients, from one to 10 pg/ml, this could have significant clinical implications. A small increase in baseline TNFα levels could easily increase the probability of case level depressive symptoms after surgery. Eight is suggested as the threshold indicative of possible or probable depression on the HADS-D[58]. Following these guidelines, an increase of one pg/ml in TNFα levels increases the odds of case level depressive symptoms by two (confidence interval 1.16 to 3.46). However, this is not as clinically significant as a PH of depression, which is associated with an increase of five points on the HADS-D and a decrease of 14 on the global QoL scale: both of which would be interpreted as clinically significant.

The evidence towards the association between PH depression, LE, CT, NE and increased inflammation is of relevance to patient treatment outcome. Previous papers[146, 181] and the findings from this thesis have shown a high correlation between depressive symptoms and poorer QoL. This study also found a direct association between the investigated factors and poorer QoL. The fact that these factors were rarely associated with poorer QoL in the adjusted models in chapter 10 suggests that the association between the investigated markers and QoL is mediated by depressive symptoms.

The association between increased inflammation and depressive symptoms is of special interest given the association between inflammation and cancer survival. However, it is already well documented that individuals suffering from a DD are at increased risk of all cause mortality[72]. Moreover, one study that found a relationship between increased mortality in cancer patients with a DD, reported that the increased mortality was comparable to that of patients with a DD but no cancer[354]. Similarly, increased inflammation has been associated with increased all cause mortality (even after excluding cardiovascular deaths) in general population samples[355], and this increased risk is not significantly greater in cancer patients[144]. This suggests that any reported associations between depression,

inflammation and decreased cancer survival may not be related to the effect of inflammation on tumour progression. Although, a primary care intervention aimed at improving treatment of depression in older general practice patients resulted in decreased mortality that was mainly attributable to a decrease in cancer deaths in the intervention arm[356]. Nevertheless, there are many possible reasons why comorbid depression may increase cancer mortality: patients with comorbid MD and cancer are known to be less compliant with treatment; in the case of HN cancer, patients show less adherence to smoking cessation programmes[149, 150] and there is some evidence of an association between depression and later presentation of cancer, therefore greater disease[357]. Thus, if the association between depression and inflammation is related to increased mortality, it is almost surprising that there is not more robust evidence of increased mortality in cancer patients with a DD. However, at present the association is still very much under debate (see Coyne *et al*. (2007)[358], comment by Spiegel and Kraemer[359] and author reply[360]).

11.2.2 Future treatment of cancer patients

Despite the increased risk of a DE and the fact that mental health specialists continue to raise awareness of this risk, depression remains under diagnosed and under treated[6, 7, 347]. In one interesting study, patients were asked what they would most like the surgeon to attend to on a clinic visit and also asked the surgeons to rate what they think is important to the patients from a list of possible answers[361]. They found that whilst 26% of cancer patients wanted surgeons to attend to their emotional state, none of the surgeons thought that this was important to the patients. This shows just how important it is to continue alerting clinicians to the psychological impact of cancer. Given the time constraints in most clinics, easy screening techniques may be of interest to surgeons.

This study found the prevalence of depression to be slightly higher than that of the general population. This is most likely because those that are at risk for

depression (e.g. have a PH of depression) often experience a recurrent episode soon after their cancer diagnosis. Higher rates of DE have been found in breast cancer patients around the time of diagnosis[362]. However, if patients with a recurrent DD were excluded, there was no evidence of a higher prevalence of new DEs when compared to an age matched control sample[362]. Therefore, PH depression is a simple and useful way of identifying patients at high risk of a DE soon after a cancer diagnosis.

The findings that baseline information such as PH depression, other LE, NE and CT are associated with increased depressive symptomatology are also clinically useful. That PH depression is so highly associated with increased risk of a DD is especially relevant as it would only involve one extra screening question at the first presentation to a cancer clinic. Although the predictive value of PH depression is greatest when using a PH depression as rated by a diagnostic interview, the findings from the cross sectional study suggest that asking whether the patient has received past treatment for depression is also an effective way of assessing whether a patient is at increased risk of a DE. This question could be incorporated into a medical history questionnaire which is often used in cancer clinics at the first patient visit. This could prove very useful, especially given the reported reservations of screening efficacy[125]. Even so, depressive symptoms at baseline have been found to be important in prediction of later QoL[363].

The robust finding of an association between LE and increased depressive symptoms, DE6 and poorer QoL also suggests that it is important to consider the social situation of cancer patients. Training oncology staff in psychiatric interviewing has been shown to help staff identify those with a DD in the training setting[364]. However, they did not report whether this training resulted in a higher proportion of patients with depression being identified. Nevertheless, a number of interventions may help identify those at increased risk of a DE soon after their cancer diagnosis: 1) clinicians showing increased awareness of patients' emotional state, 2) brief training regimes for the nursing staff; but mostly 3) increased

awareness of psychological markers for depression in cancer patients, especially the use of a past mental health screening question.

Increased identification is particularly important because depression in cancer patients is readily treatable. Although the type of treatment is dependent on clinic resources, pharmacological and psychosocial interventions have all been shown to be useful[365]. Pharmacological treatment has been shown to be effective in treating depression even in terminally ill cancer patients[365, 366]. Psychological therapies, such as supportive group therapy[367] and mindfulness[368] have also proved to be effective in increasing QoL[369]. Moreover, psychological interventions not only reduced depressive symptoms, but also pain, fatigue and inflammation in breast cancer patients[370]. Alternative medicine interventions have also been used; Qigong has been shown to improve QoL and reduce fatigue and CRP levels in cancer patients[371]. Similarly, yoga has been shown to reduce anxiety and depression and cortisol levels in cancer patients[372]. In addition, treatment with anti-depressants has been shown to reduce depressive symptoms in cancer patients and increase compliance to chemotherapy or hormone treatment in breast cancer patients[373]. Prophylactic treatment with anti-depressants has also been shown to decrease the risk of developing depression in HN cancer patients with greater than stage II tumours[374]. However, given the side effects to anti-depressants, this may be considered unethical. Whilst the information is useful when considered in context with the other findings, the prophylactic treatment of all patients is not recommended.

Reduction of depressive symptoms and inflammation is especially appealing as reducing inflammatory markers is likely to lead to lower levels of sickness behaviour, such as increased pain and fatigue that is reported in this study. Very little work has been done on anti-inflammatory treatments in cancer patients, but early stage clinical trials have shown some promising results with respect to reducing inflammation and cancer related symptoms[375]. It is also worth considering treatment regimes, for instance using local anaesthetic as well as

general anaesthetic for operating on CR cancer patients resulted in a suppressed post operative cytokine surge[376]. Patients who received local anaesthetic during their operation were also quicker to start eating post surgery and required less post operative pain relief.

Whilst this section has focused on possible improvements to cancer care, it is important to note that the level of cancer care in the two clinics was consistently very good. For instance, the HN cancer multi-disciplinary team always considered the patients' social situations and the cancer nurse specialists were very aware of the emotional implications of a cancer diagnosis. However, both clinics were limited by resources, so anything that would help identify at risk patients would help, as would knowledge about possible treatments. Previous work in other clinics found 26% of female cancer patients and 11% of male cancer patients would have liked a social support intervention[377]. These results were not mediated by depressive symptoms. However, whilst the data from this study showed some robust and consistent findings, as a result of the close interaction with individual patients, it was also apparent that each patient was very different. Even if each difference could be measured, it would be unfeasible to consider every aspect of each patient. This suggests that holistic and patient oriented approaches, where the patient has more control over their own care, would be the most beneficial. Very broad approaches, which include lectures, nutritional information, exercise classes, support sessions have proven to be very popular[378].

11.3 Scientific implications

This thesis has demonstrated how factors unrelated to the cancer diagnosis influence cancer patients' treatment outcome with respect to their QoL. Childhood trauma, NE, LE and PH depression were all associated with increased depressive symptoms and poorer QoL. In many cases, this risk appeared to be even higher between one and three months post operatively. Also, all but CT were associated with an increased risk of a DE6. These psychological markers were associated

with increased self rated symptoms of pain and fatigue. Notably, this thesis also found a relationship between inflammation and later depressive symptoms in CR cancer patients. This is important as it shows a potential physiological mechanism to psychological symptoms and adds to the current understanding of mind and body interactions. Even so, patients' QoL and depressive symptoms returned to near baseline by six months irrespective of the factors unrelated to their cancer diagnosis. This study showed that there are important interrelations between vulnerability to a DD, inflammation, depressive symptoms and poorer QoL, and these relationships are especially important soon after a cancer diagnosis. Further work on the relationship between inflammation and mood in cancer patients at later stages of the illness is recommended.

This study also found substantially more significant results in the CR cancer patient group compared to the HN cancer patient group. As the CR group was considerably smaller than the HN group, this is most likely due to greater homogeneity in the CR group. This supports the need for homogenous samples in cancer research – especially when investigating inflammatory markers, given the number of factors that affect cytokine levels.

11.4 Methodological evaluation

11.4.1 Measures

The CTQ, EPQ and LE may all have been affected by recall bias which was discussed in chapter 7 on the role of psychological factors.

11.4.1.1 Childhood trauma

Using the total score of the CTQ resulted in greater sensitivity to CT, but less specificity. This is useful in a pilot study (such as this) as it gives more power, especially since the measures of abuse and neglect are often associated with each other. However, some of the findings relating to CT were inconsistent, suggesting

that either the relationship varies according to the type of trauma or the results are unreliable. Further studies with larger samples could help clarify this. Also, the CTQ only measures some forms of chronic ELS, not other forms, such as parental illness and no acute trauma (e.g. parental loss, accident, early illness). However, a study that included parental loss, physical illness and economic adversity found they were not associated with development of a mood disorder after adjusting for family conflict (such as parental mental illness and abuse or neglect)[379]. In contrast, the different types of abuse and neglect were all associated with increased risk of a mood disorder even after adjusting for all the other types[379]. This suggests that the CTQ may have covered most of the possible risk factors. Thus, where a prospective measure is not available, the CTQ is a quick and comprehensive validated tool to assess for the importance of ELS.

11.4.1.2 Neuroticism

Whilst the EPQ is considered a reliable measure of NE, the use of NE for prediction of psychopathology has been heavily criticised[228]. There is little doubt that NE scores correlate highly with depressive symptoms[228, 380]. Neuroticism also mediates much of the genetic risk of a DD[62] and is associated with increased risk of numerous psychopathologies and psychosomatic disorders (see Ormel et al, 2004[228]). Neuroticism also correlates with PH of mental illness and family history of mental illness[380]. However, previous studies have also shown that levels of NE decrease after recovery from a DE (see McWilliams, 2003[344]). Thus it has been proposed as merely a “pseudo” depression measure, simply measuring the average level of distress over a period of time[228]. Neuroticism would therefore often be reported as related to risk of DE and personal and family history of mood disorders, but more closely relate to current depressive symptoms. However, other studies have shown that there appear to be trait and state like properties to the personality measure[344]; suggesting that the trait level could confer a useful indication of risk. Nevertheless, questionnaires assessing NE are much longer than the average depressive symptom questionnaire and, given the high

correlation, it may well be simpler to rely on level of depressive symptoms – depending on the degree of variation in the NE scores.

11.4.1.3 Life events

Although the BLEQ may be influenced by current mood, the number of LE around the time of diagnosis was a useful marker of psychological distress and poorer QoL. Using the rating of the LE did not add to the explanatory power of the BLEQ, so future work may consider omitting the extra questions.

11.4.1.4 Coping

There was limited consistency in the coping results. The relationship between coping strategies, depressive symptoms and poorer QoL varied a lot over time and between patient samples, which may be because of the fluctuations in mood over time and the differences in the patient samples. However, the questionnaire was very long and gave insufficient significant results to be considered in future research, although the humour question is probably worth keeping. On the other hand, there is much more evidence of an association between increased social support and greater QoL[55, 214, 381]. In addition, social attachment and seeking instrumental support have both been linked to lower levels of IL6 in cancer patients[119, 120]. Thus a measure of social support may be more informative.

11.4.1.5 Schedules for Clinical Assessment in Neuropsychiatry and Hospital Anxiety and Depression Scale

The SCAN gave diagnoses according to both ICD-10 and DSM-IV criteria, which was useful in determining borderline patients. This is especially useful given the difficulty in assessing depression in cancer patients. As discussed in chapter 1, using different diagnostic criteria leads to a lot of variation in the prevalence of DD[382]. Also, this study included any diagnosis of depression, but in future work, separation of any cases that appear to be secondary to pain, given the high

association between pain and depression, may be useful. Due to a high correlation between pain and depression in many studies and longer pain duration being associated with increased risk of a DE, some postulate that pain and depression are interrelated[383]. As a result, depression relating to cancer pain may be aetiologically distinct from depression in cancer patients with less pain.

Secondly, the SCAN rarely gave a PH or current diagnosis of anxiety and it would be worth comparing the anxiety ratings in the SCAN to that of other clinical interviews.

The HADS was well tolerated by patients and showed good reliability. In some respects, it would be more useful to have used the HADS as a categorical measure, choosing a threshold of eight or eleven as case level depression[58]. However, using the HADS categorically is dependent on trusting the reliability of the decreed threshold. Whilst the authors of the HADS suggest a threshold of eight (which is often used)[58], studies in HN cancer patients have found a threshold of five is the optimal threshold for detection of a possible DE[130]. Moreover, relatively few patients scored above the threshold of eight for case level depression or anxiety, which would have resulted in reduced power. Finally, the use of the threshold is normally to indicate a DD, which was already assessed here, so using the HADS as a scale gave greater sensitivity.

11.4.1.6 European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire

Despite some studies showing that QoL measures compare equally to other medical measures in terms of the degree of measurement error[384], there are still a number of limitations to the self report method.

With regard to the self reported symptom items, previous studies have shown that cancer patients with depression report higher levels of symptoms[385]. Also, levels

of NE correlate with greater symptom reporting, but not to objective measures of symptoms[228]. This evidence suggests that those with a DD are more likely to report symptoms, but may not show increased symptom levels when assessed with more objective measures. However, self ratings of swallowing function have been shown to correlate with objective measures (such as Barium swallow test) in HN cancer patients[177]. There is a large overlap between fatigue and pain and some other cancer related symptoms (e.g. loss of appetite)[343, 383] and depression, therefore it is tricky to interpret the findings when fatigue is included in the model. Thus, the self rated nature of the questionnaires means it is harder to tell what aspects are influenced by mood and what are more objective impairments. It would be interesting to test for more objective measures of symptoms, but if the rating scale offers a measure of symptom perception this should also be considered a useful measure.

The study is limited by the use of the global QoL scale for a dependent variable. The scale only consists of two seven item measures where a single point change could be interpreted as resulting in a clinically significant change (see section 11.2). Also, patients with depression, both in the general population and in cancer samples, have been shown to report lower QoL, but show equivocal QoL when assessed by more objective measures[148, 386]. Self rated QoL is important, as the subjective nature of the report is valuable. However, the two item scale of the EORTC-QLQ does not provide much sensitivity, so future work may benefit from a more detailed generic QoL measure with a total score, which would give a broader view of patients' QoL and result in a more sensitive measure. This could also be combined with more objective functional assessments.

11.4.1.7 Physiological assessments

The cortisol results suggest that cortisol measures would be of little clinical value. This is especially true given that patients tended to be more concerned about the

saliva samples compared to providing blood samples, probably due to the extra cognitive demand and responsibility required for the saliva samples.

The findings on inflammation were interesting and suggest that the relationship between TNFα and depressive symptoms is worthy of further investigation. As discussed in chapter 8, other cytokines, such as IL-10, may also be worth including in further analyses.

11.4.2 Protocol

11.4.2.1 Timing of questionnaires

The timing of questionnaires at three months post surgery (T4) may have confounded the results. Some of the psychological variables are associated with a further increase in depressive symptoms at this time point (see chapter 7). However, there were actually fewer associations between inflammation and pain at this point despite associations at one and six month post surgery (see chapter 9). This may be because T4 is associated with increased vulnerability to depression compared to other time points; past research suggests that depressive symptoms are at their highest at two to three months after diagnosis[124]. Thus, it is hard to say whether the increased association between the psychological variables and depressive symptoms at T4 is due to the timing of the questionnaires, or because those that are vulnerable to low mood are especially susceptible to lowered mood at three months. Also, for some patients, they may have just finished a course of adjuvant therapy which could have an emotional impact. It was decided to assess the psychological variables at this time point as it was thought unethical to burden the patients around the time of their diagnosis and treatment, but leaving them until the end of the study would risk lower completion rates due to sample attrition. However, given these results, future studies could consider moving this assessment to another time point.

11.4.2.2 Analysis

Due to the small sample size and multiple testing there is a risk of both type I and type II errors. Also, complete case analysis may have led to biases because the patients that remained in the study were healthier than those who did not. Also, the chosen analysis may be considered over complicated given the sample size. However, these analyses were chosen in order to cope with the smaller sample size, for instance two analysis methods had to be significant in order to interpret a finding as significant in the cytokine analyses. Colinearity between many of the variables also resulted in a much more complicated multivariate analysis, as including many of these measures would lead to over fitting a model. Whilst the more complicated analyses were considered necessary in order to ensure reliable results, more complicated analyses can make results harder to interpret. Future work with larger samples is less likely to require multiple testing methods and could use imputation to reduce the biases from missing data.

11.4.2.3 Methodology

The findings of the study are limited as they are only applicable to curative CR and HN cancer patients who undergo surgical treatment. The study appears to be further limited by the heterogeneity of the HN cancer patients; previous studies have found large differences in QoL and symptoms by type of HN cancer[146]. This highlights the need for more homogenous groups in research.

Also, due to the smaller sample, some aspects of QoL could not be fully investigated in the adjusted models, despite initial findings of a strong correlation between some symptoms and poorer global QoL. For example, very few patients had stomas, but stoma problems were very often associated with poorer QoL (see chapter 4 and chapter 10). Although as reported in chapter 1, a meta-analysis found no difference in QoL between patients with and without a colostomy bag, studies continue to report significantly poorer QoL in patients with a stoma[173, 387].

In addition, studies have reported high levels of stoma problems in those with stomas[388], with up to 80% of patients still struggling with some aspects of stoma function up to two years post treatment. However, it would be very hard to represent properly this confounding factor in a study investigating inflammation and QoL in cancer patients due to the large numbers it would require.

11.5 Practical applications and recommendations

11.5.1 Research

Further work on this data set could include more investigations into the correlation of depressive symptoms and QoL. Despite the longitudinal nature of the study, none of the results indicate causality with respect to the relationship between increased depressive symptoms and poorer QoL. Whilst the relationship is most likely to be bidirectional, a time lagged analysis of the data may indicate whether the depressive symptoms are a stronger predictor of poorer QoL than vice versa. Further work on this data set could include investigating the impact of extraversion on depressive symptoms and QoL.

Further research projects should involve larger, more homogeneous samples. These studies would take longer to carry out, but would result in more reliable data. Also, the studies would benefit from following patients for a full year from diagnosis, as past research has shown that it takes up to a year for QoL to return to baseline levels[146, 172]. Beyond one year of follow up is less likely to be beneficial, as studies have reported few differences in QoL between one and three years post diagnosis[177]. These projects may benefit from using a different QoL measure either instead of or as well as the EORTC-QLQ. Also, the questionnaires on personality and CT should be issued at a later time point. Moreover, social support measures may prove a more informative marker of depression than the current coping assessment. It would also be worth considering assessing IL10 levels instead of IL1ß levels, given the low levels of IL1ß that were found in this sample. Finally, larger samples would allow for multiple imputation which would be

a more reliable way to deal with missing data than complete case analysis. Really large samples would also allow for structural equation modeling, which could help identify exactly how vulnerability to DD, self reported symptoms and depressive symptoms relate to QoL.

11.5.2 Clinical

The study suggests that asking patients about PH of depression at their first visit to the clinic may help clinicians identify patients at increased risk of a DD. The study also shows how important non cancer related issues are to risk of a DE6 and cancer patients' QoL. This indicates that any moves towards more holistic and patient centered health care would benefit patients.

11.6 Summary

This thesis sought to identify psychological and physiological markers for depression in colorectal and head and neck cancer patients. Depression has been shown to be under diagnosed and under treated in cancer clinics, despite being associated with poorer treatment outcome in terms of poorer quality of life and some evidence of increased mortality. Two studies were conducted on colorectal cancer patients attending the colorectal clinic at The Royal London Hospital and in head and neck cancer patients attending the head and neck clinic at St Bartholomew's Hospital. One study was cross sectional and the other was prospective in design. The results show the prevalence of a depressive episode was higher than that of the general population in the head and neck clinic, but comparable to the prevalence in the general population in the colorectal clinic. Both studies found a strong association between increased depressive symptoms and poorer quality of life in both groups of cancer patients.

Results from the prospective study found that past history of depression, neuroticism and number of stressful life events were all important factors in predicting high depressive symptoms and risk of a depressive episode within six

months after diagnosis. These factors were more closely related to risk of a depressive episode than any cancer related symptom. Childhood trauma was also related to increased depressive symptoms and poorer quality of life. Importantly, increased inflammation before treatment in colorectal cancer patients was associated with increased depressive symptoms at one and three months post surgery. This not only adds to the literature on a link between physical and mental illness, but may also offer a rationale for the development of anti-inflammatory therapeutic agents. Also, the results suggest that inflammation and psychological risk markers for depression are very closely related to mood and self rated symptoms of fatigue and pain and it would be hard to separate the relationship between each of the factors.

The results show that it is necessary to consider all the psychological and physiological aspects of cancer patients during their cancer treatment. Cancer clinicians and other researchers would benefit from increased awareness of the close relationship between physiological and psychological aspects of cancer. Further research on inflammation and depression could increase the understanding of the relationship between physiology and mood, although, as this study demonstrates, it is hard to separate the two. Along with parallel research into the links between the mind and the body, such research should contribute to a more holistic health care approach and help reduce the divide between mental and physical health.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Appendices

Appendix 1. 1: Prevalence of depression in colorectal cancer patients

Study	N	Patients	Method	Time of assessment	% MDD
Pugliese et al.	98	Italian advanced chemo patients, with liver metastases	Semi structured interview to DSM-IIIR (unclear which interview)	Before treatment and at 18 weeks	0
Fujita et al.	36	Japanese gastrectomy abdominal patients	HADS, plus psychiatric exam on those >7	Before treatment and one year post operation	6

Prevalence of MDD in CR cancer patients.

Study	N	Patients	Method	Criteria	Time of assessment	'Case level' depressive symptoms
Richardson et al.	47	American rectal patients with colostomy	BDI	>13	1-3 months post treatment	6
Alacacioglu et al.	110	Turkish colorectal undergoing chemotherapy	BDI	>16	During treatment	24
Kurtz et al.	154	Mid western American colorectal	CES-D	>15	Diagnosis	18.2
Ramsey et al.	227	American most stage II colon	CES-D	>15	Over 5 years post diagnosis	14
Simon et al.	128	Colorectal including palliative	CES-D	>12	Average 257 days post diagnosis	14

Part one of prevalence of case level depressive symptoms in CR cancer patients. BDI= Beck Depression Inventory; CES-D=Centre for Epidemiologic Studies Depression Scale

Appendix 2. 1: Hospital Anxiety and Depression Scale

Subject name

Date of completion

Please answer the following questions with respect to how you have felt in the last week.
Underline one answer only in each section

1. I feel tense or wound up:
   - Most of the time
   - A lot of the time
   - Time to time, occasionally
   - Not at all

2. I still enjoy the things I used to enjoy:
   - Definitely as much
   - Not quite as much
   - Only a little
   - Hardly at all

3. I get a sort of frightened feeling, something awful is about to happen:
   - Very definitely and quite badly
   - Yes, but not too badly
   - A little, but it doesn't worry me
   - Not at all

4. I feel slowed down:
   - Nearly all the time
   - Very often
   - Sometimes
   - Not at all

5. I get a sort of frightened feeling like butterflies in the stomach:
   - Not at all
   - Occasionally
   - Quite often
   - Very often

6. I have lost interest in my appearance:
   - Definitely
   - I don't take as much care as I should
   - I may not take quite as much care
   - I take just as much care as ever

7. I can laugh and see the funny side of things:
   - As much as I always could
   - Not quite as much now
   - Definitely not so much now
   - Not at all

8. Worrying thoughts go through my mind:
   - A great deal of the time
   - A lot of the time
   - From time to time but not too often
   - Only occasionally

9. I feel cheerful:
   - Not at all
   - Not often
   - Sometimes
   - Most of the time

10. I can sit at ease and feel relaxed:
   - Definitely
   - Usually
   - Not often
   - Not at all

11. I feel restless as I often have to be on the move:
   - Very much indeed
   - Quite a lot
   - Not very much
   - Not at all

12. I look forward with enjoyment to things:
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

13. I get sudden feelings of panic:
   - Very often indeed
   - Quite often
   - Not very often
   - Not at all

14. I can enjoy a good book or radio or TV programme:
   - Often
   - Sometimes
   - Not often
   - Very seldom

Thank you for completing this questionnaire

Appendix 2. 2 : European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 2. 3: Colorectal CR29 QLQ module

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

Appendix 2. 4: Head and neck 35 QLQ module

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Appendix 3. 1: Past mental health screening questionnaire – colorectal patients

Barts and The London
School of Medicine and Dentistry

COLORECTAL CLINIC QUESTIONNAIRE

Dear Patient,

We are interested in studying how mood can affect the well-being and quality of life of our patients so we can improve services in this clinic. We are collecting information on your current and past mood. These questionnaires are being distributed to all patients who attend the Colorectal Clinic at The Royal London Hospital on a Thursday morning. This is to investigate what proportion of patients are suffering from mental distress and how this affects well-being, quality of life and outcome of treatment. This information will be used for research purposes to help develop ways of improving patient care.

We would be very grateful if you could complete the enclosed questionnaires and return them to us in the box provided at the front of the clinic. These questionnaires should take no more then 15 minutes of your time, all of the information you provide will be completely confidential and will only be seen by members of your clinical care team who are conducting this study.

Please feel free to contact us at the address or telephone number given below if you have any further questions relating to this survey.

Thank you for your help,

With best wishes,

Professor Sina Dorudi Consultant colorectal surgeon
Professor Ania Korszun Consultant psychiatrist
and Jo Archer Clinical assistant

Wolfson Institute of Preventive Medicine
Centre for Psychiatry
Room 105, Old Anatomy Building
Queen Mary, University of London
Charterhouse Square EC1M 6BQ
Tel: 020 7882 2039

Version 2 19/05/2008

COLRECTAL CLINIC QUESTIONNAIRE

Please complete as much as you can of the following questionnaire and feel free to write comments in the margins.

Name.....Date of Birth.....
Hospital number.....

Please circle Yes or No to the following questions:

1. Have you ever been treated for depression? YES NO
If so, please say what year(s).....

2. Have you ever been treated for anxiety? YES NO
If so, please say what year(s).....

3. Have you ever been prescribed anti-depressants? YES NO
If so, please say what year(s).....

4. Do you think you have ever suffered from depression? YES NO
If so, please say what year(s).....

5. Do you think you have ever suffered from anxiety? YES NO
If so, please say what year(s).....

5. Would you be willing to speak to a researcher on the phone for about 15 minutes to discuss any of your answers to the above questions?
YES NO

If yes, please provide a phone number and the most convenient time for someone to call:
Phone no.....
Best time(s).....

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Version 2 19/05/2008

Appendix 3. 2: Past mental health screening questionnaire – head and neck patients

mouth jaws face neck | oral & maxillo facial surgery

Barts and The London School of Medicine and Dentistry

HEAD AND NECK CLINIC QUESTIONNAIRE

Dear Patient,

We are interested in studying how mood can affect the well-being and quality of life of our patients so we can improve services in this clinic. You may remember previously completing a questionnaire in the clinic about your mood and quality of life and we are now collecting further information on your past mood.

These questionnaires are being distributed to all patients who attend the Head and Neck Clinic at St Bartholomew's Hospital on a Wednesday afternoon. This is to investigate what proportion of patients are suffering from mental distress and how this affects their well-being, quality of life and outcome of treatment. This information will be used for research purposes to help develop ways of improving patient care.

We would be very grateful if you could complete the questionnaires and return them to us in the FREEPOST envelope provided. These questionnaires should take no more then 15 minutes of your time, all of the information you provide will be completely confidential and will only be seen by members of your clinical care team who are conducting this study.

Please feel free to contact us at the address or telephone number given below if you have any further questions relating to this survey.

Thank you for your help,

With best wishes,

Professor Iain Hutchison OMFS director
Professor Ania Korszun Consultant Psychiatrist
and
Jo Archer Clinical Assistant

Wolfson Institute of Preventive Medicine
Centre for Psychiatry
Room 105, Old Anatomy Building
Queen Mary, University of London
Charterhouse Square EC1M 6BQ
Tel: 020 7882 2039

Version 2 19/05/08

mouth jaws face neck | oral & maxillo facial surgery

Barts and The London School of Medicine and Dentistry

HEAD AND NECK CLINIC QUESTIONNAIRE
Please complete as much as you can of the following questionnaire and feel free to write comments in the margins.

Name.....Date of Birth.....
Hospital number.....

Please circle Yes or No to the following questions:

1. Have you ever been treated for depression? YES NO
If so, please say what year(s).....

2. Have you ever been treated for anxiety? YES NO
If so, please say what year(s).....

3. Have you ever been prescribed anti-depressants? YES NO
If so, please say what year(s).....

4. Do you think you have ever suffered from depression? YES NO
If so, please say what year(s).....

5. Do you think you have ever suffered from anxiety? YES NO
If so, please say what year(s).....

5. Would you be willing to speak to a researcher on the phone for about 15 minutes to discuss any of your answers to the above questions?
YES NO

If yes, please provide a phone number and the most convenient time for someone to call:
Phone no.....
Best time(s).....

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Version 2 19/05/08

Appendix 5. 1: Patient information sheet

12/10/2007

Patient Information Leaflet – Version 4

1. Study title

Psychological Predictors of Well-Being in Head and Neck Cancer and Gastrointestinal and Pancreatic Cancer Patients.

2. Invitation to take part

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully. If you wish, you can discuss the information with others and our research staff will also be happy to help you if necessary. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

3. What is the purpose of the study?

The aim of our study is to identify what factors predict well-being in patients with cancer. Having an illness such as cancer can be stressful and in some people this can lead to feelings of depression and anxiety. There are various factors that contribute to making certain people more vulnerable to depression. For example, people who develop depression produce more stress hormone (cortisol) than those who do not. There are also other factors that play a part such as different ways of coping with problems or the influence of past experiences. In our study, we will look at psychological and physiological factors that can be used to predict depression in cancer patients. We will also investigate the kind of effect that emotional well-being has on the response to treatment and quality of life. The psychological factors will be assessed by questionnaires and a short interview. Physiological factors will be assessed by measuring salivary biomarkers, e.g cortisol and blood plasma C-reactive protein and cytokine levels. C-reactive protein and cytokines are messenger molecules that are involved in your immune response, people with depression may show elevated levels of certain cytokines. Some of your saliva may also be used in another experiment to test for a relationship between two different biomarkers. If this is the case, the same patient confidentiality would apply.

4. Do I have to take part?

There is absolutely no obligation for you to take part in this study. It is completely up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you decide not to take part in this trial, your doctors and surgeons will continue to treat you as they would normally.

5. What will happen to me if I decide to take part?

All of your treatment will follow the normal standard procedures.

1

12/10/2007

In addition to your treatment, on joining you will be asked to complete two brief questionnaires. Each of these questionnaires will take no more than 10 minutes to complete.

We will also ask you if we can take a small sample of blood (about 2 teaspoons) one week before your treatment starts. We will ask you for another sample of blood one week and four weeks after treatment. Taking each sample of blood will take very little time, but it has to be taken at a particular time of day so we will try and fit this in on a day convenient to you. Also, the samples can be taken at your house or at the clinic and if you decide to come into the clinic then we will reimburse your travel expenses.

You will be asked to give some saliva samples and you will be given information on how to do this. You will be asked to collect saliva samples by chewing on a small cotton roll for one minute and then placing this in the tube provided. You will be asked to do this first thing in the morning and in the evening for three consecutive days. You will be given detailed information on the collection and all the equipment will be supplied together with a prepaid envelope which you can use to return the samples to us. You will be able to phone the research assistant at any time if you feel unsure what to do.

One month afterwards you will be asked to see a researcher during one of your clinic appointments to fill in three more questionnaires, which should take no more than 20 minutes in total. At three months we will ask you to repeat two of those questionnaires, you will also receive a pack containing 3 more questionnaires which you will be free to complete at home at your own convenience. You will also be asked to choose a time and place within the next month to take part in an interview which will take no more than one hour of your time. The interview may take place at your house, at the clinic or on the phone; if you would prefer to come to us then we can reimburse you for travel expenses. The interview will take up to 45 minutes and will focus on your past mental health.

Finally at six months you will be asked once more to repeat those questionnaires and you will be asked to fill in an additional questionnaire. Again, we will try and fit all of this in with your routine visits to the clinic.

It may be necessary for us to check some details of your medical history; therefore we will also ask you to consent to giving us access to your medical records at Barts and The London and to your GP records. Any information obtained from your records will remain strictly confidential.

You may choose to take part in only some components of the study. You can choose not to take part in the cortisol or cytokine (blood sampling) parts of the study.

6. What will happen to any samples I give?

The saliva samples you give will be frozen and stored in a laboratory until they are ready to be analysed for cortisol levels, all of your samples will be stored with a code number that does not contain any details about you but it will be possible for us to link the specimen with your study details. After analysis the samples that you give will be destroyed and will not be used in any other research. Similarly the blood sample you

give will be frozen until it is ready to be analysed for cytokine levels. After the analyses any surplus samples will be destroyed and will not be used in any other research.

7. What will happen to the data collected?

The results from your questionnaires and the interview will also be stored with a code number that does not contain any details about you but it will be possible to link all of your data for the purpose of comparing your results. All of the data will be stored in locked filing cabinets, or kept on password protected computers. No one but the people involved in this study will have access to your data.

8. What do I have to do?

Apart from the time you spend completing the questionnaires and the interview, and giving the blood and saliva samples, being in the study will not place any restrictions on your lifestyle. For example, you can drive, drink and play sport as normal. You can also take regular medication.
We will try to fit the interview and questionnaires in with your clinical appointments. However, if necessary we will make home visits or reimburse travel expenses.

9. What are the possible disadvantages of taking part?

There are no risks in taking part in the study. You will be giving some of your time to the study to fill in the questionnaires, take part in the interview and to give the saliva samples and blood sample. However, all of these components to the study will be arranged to fit in with your lifestyle.

10. What are the possible benefits of taking part?

There is no direct benefit to you. The purpose of the study is to provide information on different risk factors for depression; hopefully this will lead to improvements in the ways future patients are treated.

11. What if new information becomes available?

Sometimes during the course of a research project new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study - if you decide to withdraw this will not affect your treatment in any way.

12. What happens when the research study stops?

Once the study has been completed you will continue to be seen by your doctor or surgeon as part of your routine care. Your data may be used for a number of years after you have finished participating in the study.

13. What if something goes wrong?

You should not encounter any additional risks due to taking part in the study, however, Barts and The London Queen Mary's School of Medicine and Dentistry has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities an injury was caused as a direct result of the intervention or procedures involved in the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

14. Will my taking part in the study be kept confidential?

If you consent to take part in this study, all information collected about you during the course of the study will be kept strictly confidential. The information gathered in this trial will be coded so that no one will be able to identify you from the data that will be used in the analyses. Also, only the people involved in this study will have access to these data. We will ask your permission to inform your GP of your participation in the study. We may request your permission to register you details with the Office for National Statistics (ONS) so that we may follow your health status.

15. What will happen to the results of the research study?

The results from the study will be published in medical and scientific journals. You will not be identified in any report or publication arising from this study. There may also be a presentation at Saving Faces or other user groups to which you will be invited to attend.

16. Who is organising and funding the research?

This research is funded by Saving Faces and the Special Trustees Royal London and St Bartholomew's Foundation. Researchers at Queen Mary University of London are organising the research with the cooperation of the surgeons at participating cancer clinics. The doctors and surgeons will not receive any special or additional payment if you agree to participate in the study.

17. Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by Barts and The London Local Research Ethics Committee.

18. Contacts for further information

If you have any questions or concerns about this study please contact your consultant or Jo Archer, one of the research staff based at Queen Mary's.

Research staff – Jo Archer
Phone no. 020 7882 2039
Email j.a.archer@qmul.ac.uk

Chief Investigator – Prof Ania Korszun
Phone no. 020 7882 2028

12/10/2007

Consultant Surgeon and Clinical Director – Mr Iain Hutchison
Phone no. 07889 473 916

For impartial information on patient research please contact:
Patient Advisory Liaison Service (PALS). Tel: 020 7377 6335 or email pals@bartsandthelondon.nhs.uk

CancerHelp UK provides general information for patients about cancer and its treatment on their website, www.cancerhelp.org.uk

Cancer Research UK has cancer information nurses who provide a confidential service. Twl: 020 7061 8355 or email: cancer.info@cancer.org.uk

Cancer BACUP provides support and counselling to help people living with cancer, Tel: 0808 800 1234, www.cancerbacup.org

If at any point you wish to make a formal complaint you may contact:
Jarrard O'Brien
Quality Development
Barts and The London NHS Trust
Healthcare Governance Directorate
3rd Floor, Prescot Street
020 7480 4857
Jarrard.obrien@bartsandthelondon.nhs.uk
Thank you for reading this.

Appendix 5. 2: Childhood Trauma Questionnaire

CONFIDENTIAL

Protocol Code	Subject number	Date of completion

EARLY LIFE STRESS

When I was growing up….	Never true	Rarely true	Sometimes true	Often true	Very often true
1. I didn't have enough to eat.					
2. I knew that there was someone to take care of me and protect me.					
3. People in my family called me things like "stupid", "lazy" or "ugly".					
4. My parents were too drunk or high to take care of the family.					
5. There was someone in my family who helped me feel I was important or special.					
6. I had to wear dirty clothes.					
7. I felt loved.					
8. I thought that my parents wished I had never been born.					
9. I got hit so hard by someone that I had to see a doctor or go to hospital.					
10. There was nothing I wanted to change about my family.					
11. People in my family hit me so hard that it left me with bruises or marks.					
12. I was punished with a belt, a board, a cord, or some other hard object.					
13. People in my family looked out for each other.					
14. People in my family said hurtful or insulting things to me.					
15. I believe I was physically abused.					
16. I had the perfect childhood.					
17. I got hit of beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.					
18. I felt that someone in my family hated me.					
19. People in my family felt close to each other.					
20. Someone tried to touch me in a sexual way, or tried to make me touch them.					
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.					
22. I had the best family in the world.					
23. Someone tried to make me do sexual things or watch sexual things.					
24. Someone molested me.					
25. I believe that I was emotionally abused.					
26. There was someone to take me to the doctor if I needed it.					
27. I believe I was sexually abused.					
28. My family was a source of strength and support.					

Appendix 5. 3: Eysenck Personality Questionnaire

CONFIDENTIAL

Protocol Code	Subject number	Date of completion

Adult EPQ

Please answer each question by filling in the "Yes" or "No" box following the question. There are no right or wrong answers and no trick questions. Work quickly and do not think too long about the exact meaning of the questions.

1.	Do you have many different hobbies?	Yes ☐	No ☐
2.	Do you stop to think things over before doing anything?	Yes ☐	No ☐
3.	Does your mood often go up and down?	Yes ☐	No ☐
4.	Have you ever taken the praise for something you knew someone else had really done?	Yes ☐	No ☐
5.	Are you a talkative person?	Yes ☐	No ☐
6.	Would being in debt worry you?	Yes ☐	No ☐
7.	Do you ever feel miserable for no reason?	Yes ☐	No ☐
8.	Were you ever greedy by helping yourself to more than your share of anything?	Yes ☐	No ☐
9.	Do you lock your house carefully at night?	Yes ☐	No ☐
10.	Are you rather lively?	Yes ☐	No ☐
11.	Would it upset you a lot to see a child or an animal suffer?	Yes ☐	No ☐
12.	Do you often worry about things you should not have done or said?	Yes ☐	No ☐
13.	If you say you will do something, do you always keep your promise no matter how inconvenient it might be?	Yes ☐	No ☐
14.	Can you usually let yourself go and enjoy yourself at a lively party?	Yes ☐	No ☐
15.	Are you an irritable person?	Yes ☐	No ☐

Continued.....

Subject number.....

16.	Have you ever blamed someone for doing something you knew was really your fault?	Yes ☐ No ☐
17.	Do you enjoy meeting new people?	Yes ☐ No ☐
18.	Do you believe insurance schemes are a good idea?	Yes ☐ No ☐
19.	Are your feelings easily hurt?	Yes ☐ No ☐
20.	Are *all* your habits good and desirable ones?	Yes ☐ No ☐
21.	Do you tend to keep in the background on social occasions?	Yes ☐ No ☐
22.	Would you take drugs which may have strange or dangerous effects?	Yes ☐ No ☐
23.	Do you often feel 'fed-up'?	Yes ☐ No ☐
24.	Have you ever taken anything (even a pin or a button) that belonged to someone else?	Yes ☐ No ☐
25.	Do you like going out a lot?	Yes ☐ No ☐
26.	Do you enjoy hurting people you love?	Yes ☐ No ☐
27.	Are you often troubled about feelings of guilt?	Yes ☐ No ☐
28.	Do you sometimes talk about things you know nothing about?	Yes ☐ No ☐
29.	Do you prefer reading to meeting new people?	Yes ☐ No ☐
30.	Do you have enemies who want to harm you?	Yes ☐ No ☐
31.	Would you call yourself a nervous person?	Yes ☐ No ☐
32.	Do you have many friends?	Yes ☐ No ☐
33.	Do you enjoy practical jokes that can sometimes really hurt people?	Yes ☐ No ☐
34.	Are you a worrier?	Yes ☐ No ☐
35.	As a child, did you do as you were told immediately and without grumbling?	Yes ☐ No ☐

Continued.....

Subject number.....

36.	Would you call yourself happy-go-lucky?	Yes ☐	No ☐
37.	Do good manners and cleanliness matter much to you?	Yes ☐	No ☐
38.	Do you worry about awful things that might happen?	Yes ☐	No ☐
39.	Have you ever broken or lost something belonging to someone else?	Yes ☐	No ☐
40.	Do you usually take the initiative in making new friends?	Yes ☐	No ☐
41.	Would you call yourself tense or 'highly-strung'?	Yes ☐	No ☐
42.	Are you mostly quiet when you are out with other people?	Yes ☐	No ☐
43.	Do you think marriage is old-fashioned and should be done away with?	Yes ☐	No ☐
44.	Do you sometimes boast a little?	Yes ☐	No ☐
45.	Can you easily get some life into a rather dull party?	Yes ☐	No ☐
46.	Do people who drive carefully annoy you?	Yes ☐	No ☐
47.	Do you worry about your health?	Yes ☐	No ☐
48.	Have you ever said anything bad or nasty about anyone?	Yes ☐	No ☐
49.	Do you like telling jokes and funny stories to your friends?	Yes ☐	No ☐
50.	Do most things taste the same to you?	Yes ☐	No ☐
51.	As a child, were you ever cheeky to your parents?	Yes ☐	No ☐
52.	Do you like mixing with people?	Yes ☐	No ☐
53.	Does it worry you if you know there are mistakes in your work?	Yes ☐	No ☐
54.	Do you suffer from sleeplessness?	Yes ☐	No ☐
55.	Do you always wash before a meal?	Yes ☐	No ☐

Continued.....

Subject number.....

56.	Do you nearly always have a 'ready answer' when people talk to you?	Yes ☐ No ☐
57.	Do you like to arrive at appointments in plenty of time?	Yes ☐ No ☐
58.	Have you often felt listless and tired for no reason?	Yes ☐ No ☐
59.	Have you ever cheated at a game?	Yes ☐ No ☐
60.	Do you like doing things in which you have to act quickly?	Yes ☐ No ☐
61.	Is (or was) your mother a good woman?	Yes ☐ No ☐
62.	Do you often feel that life is very dull?	Yes ☐ No ☐
63.	Have you ever taken advantage of someone?	Yes ☐ No ☐
64.	Do you often take on more activities than you have time for?	Yes ☐ No ☐
65.	Are there several people who keep trying to avoid you?	Yes ☐ No ☐
66.	Do you worry a lot about your looks?	Yes ☐ No ☐
67.	Do you think people spend too much time safeguarding their future with savings and insurance?	Yes ☐ No ☐
68.	Have you ever wished you were dead?	Yes ☐ No ☐
69.	Would you dodge paying taxes if you were sure you could never be found out?	Yes ☐ No ☐
70.	Can you get a party going?	Yes ☐ No ☐
71.	Do you try not to be rude to people?	Yes ☐ No ☐
72.	Do you worry too long after an embarrassing experience?	Yes ☐ No ☐
73.	Have you ever insisted on having your own way?	Yes ☐ No ☐
74.	When you catch a train do you often arrive at the last minute?	Yes ☐ No ☐
75.	Do you suffer from 'nerves'?	Yes ☐ No ☐

Continued.....

Subject number.....

76.	Do your friendships break up easily without it being your fault?	Yes ☐	No ☐
77.	Do you often feel lonely?	Yes ☐	No ☐
78.	Do you always practice what you preach?	Yes ☐	No ☐
79.	Do you sometimes like teasing animals?	Yes ☐	No ☐
80.	Are you easily hurt when people find fault with you or the work you do?	Yes ☐	No ☐
81.	Have you ever been late for an appointment or work?	Yes ☐	No ☐
82.	Do you like plenty of bustle and excitement around you?	Yes ☐	No ☐
83.	Would you like other people to be afraid of you?	Yes ☐	No ☐
84.	Are you sometimes bubbling over with energy and sometimes very sluggish?	Yes ☐	No ☐
85.	Do you sometimes put off until tomorrow what you ought to do today?	Yes ☐	No ☐
86.	Do other people think of you as being very lively?	Yes ☐	No ☐
87.	Do people tell you a lot of lies?	Yes ☐	No ☐
88.	Are you touchy about some things?	Yes ☐	No ☐
89.	Are you always willing to admit when you have made a mistake?	Yes ☐	No ☐
90.	Would you feel sorry for an animal caught in a trap?	Yes ☐	No ☐

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL OF THE QUESTIONS

Thank you for taking the time to fill in this questionnaire.

Appendix 5. 4: Brief Life Events Questionnaire

CONFIDENTIAL

Protocol Code	Subject number	Date of completion

The Brief Life Events Questionnaire

The following questions are about events or problems which may have happened to you during the past 6 months which might have caused you distress and to seek help.

1. In the past 6 months have you suffered from a serious illness, injury or an assault? — Yes ☐ No ☐

   If yes, at the time, how bad was that for you? — Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

2. In the past 6 months has a serious illness, injury or assault happened to a close relative? — Yes ☐ No ☐

   If yes, at the time, how bad was that for you? — Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

3. In the past 6 months did a parent, spouse (or partner), child, brother or sister of yours die? — Yes ☐ No ☐

   If yes, at the time, how bad was that for you? — Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

4. In the past 6 months did a close family friend or other relative die, such as an aunt, cousin or grandparent? — Yes ☐ No ☐

   If yes, at the time, how bad was that for you? — Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

5. In the past 6 months did you have a separation due to marital difficulties or break of a steady relationship? — Yes ☐ No ☐

   If yes, at the time, how bad was that for you? — Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

Continued...

Subject number.....

6. In the past 6 months have you had a serious problem with a close friend, neighbour or relative? Yes ☐ No ☐

If yes, at the time, how bad was that for you? Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

7. In the past 6 months were you made redundant or sacked from your job? Yes ☐ No ☐

If yes, at the time, how bad was that for you? Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

8. In the past 6 months were you seeking work without success for more than one month? Yes ☐ No ☐

If yes, at the time, how bad was that for you? Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

9. In the past 6 months, did you have a major financial crisis such as losing the equivalent of three months income? Yes ☐ No ☐

If yes, at the time, how bad was that for you? Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

10. In the past 6 months have you had problems with the police involving a court appearance? Yes ☐ No ☐

If yes, at the time, how bad was that for you? Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

11. In the past 6 months was anything you valued lost or stolen? Yes ☐ No ☐

If yes, at the time, how bad was that for you? Very Bad ☐ Moderately Bad ☐ Not too Bad ☐

12. In the past 6 months did you/your wife or partner give birth to a child? Yes ☐ No ☐

If yes, how much stress do you think this caused you? Lots ☐ Quite a lot ☐ A little ☐

Continued.....

Subject number……..

13. In the past 6 months do you think anything has happened that has caused you a lot of stress?

Yes ☐ No ☐

If yes, what was it?.....
……..

14. Do you think anything has happened to you in your life that has led to you feeling depressed?

Yes ☐ No ☐

If yes, what was it?.....
……..

Thank you for taking the time to fill in this questionnaire.

Appendix 5. 5: Brief COPE

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Protocol Code	Subject number	Date of completion

These questions are about how people deal with cancer and the pain associated with it. Please answer the questions below according to your thoughts and feelings during your cancer. People's ways of dealing with cancer vary over time, but try and think about what you would **usually** do to deal with any stress from cancer. Please circle the number that best describes your response to each statement.

0= I haven't been doing this at all **3= I've been doing this a lot**

I've been concentrating my efforts on doing something about the situation I am in	0	1	2	3
I've been trying to make the situation better	0	1	2	3
I've been trying to come up with a strategy about what to do	0	1	2	3
I've been thinking hard about what steps to take	0	1	2	3
I've been trying to see it in a different light, to make it seem more positive	0	1	2	3
I've been looking for something good in what's happening	0	1	2	3
I've been accepting the reality of the fact that it has happened	0	1	2	3

Subject number……

I've been learning to live with it	0	1	2	3
I've been making jokes about it	0	1	2	3
I've been making fun of the situation	0	1	2	3
I've been trying to find comfort in my religion or spiritual beliefs	0	1	2	3
I've been praying or meditating	0	1	2	3
I've been getting emotional support from others	0	1	2	3
I've been getting comfort and understanding from someone	0	1	2	3
I've been trying to get advice or help from other people about what to do	0	1	2	3
I've been getting help and advice from other people	0	1	2	3
I've been turning to work or other activities to take my mind off things	0	1	2	3
I've been doing something to think about it less, such as going to the cinema, watching TV, reading, daydreaming, sleeping or shopping	0	1	2	3
I've been saying to myself 'this isn't real'	0	1	2	3
I've been refusing to believe that it has happened	0	1	2	3

Subject number……

I've been using alcohol or other drugs to make me feel better	0	1	2	3
I've been giving up trying to deal with it	0	1	2	3
I've been saying things to let my unpleasant feelings escape	0	1	2	3
I've been using alcohol or other drugs to help me get through it	0	1	2	3
I've been criticizing myself	0	1	2	3
I've been giving up the attempt to cope	0	1	2	3
I've been expressing my negative feelings	0	1	2	3
I've been blaming myself for things that happened	0	1	2	3

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL OF THE QUESTIONS

Thank you for taking the time to fill in this questionnaire.

Appendix 5. 6: Salivette Instructions

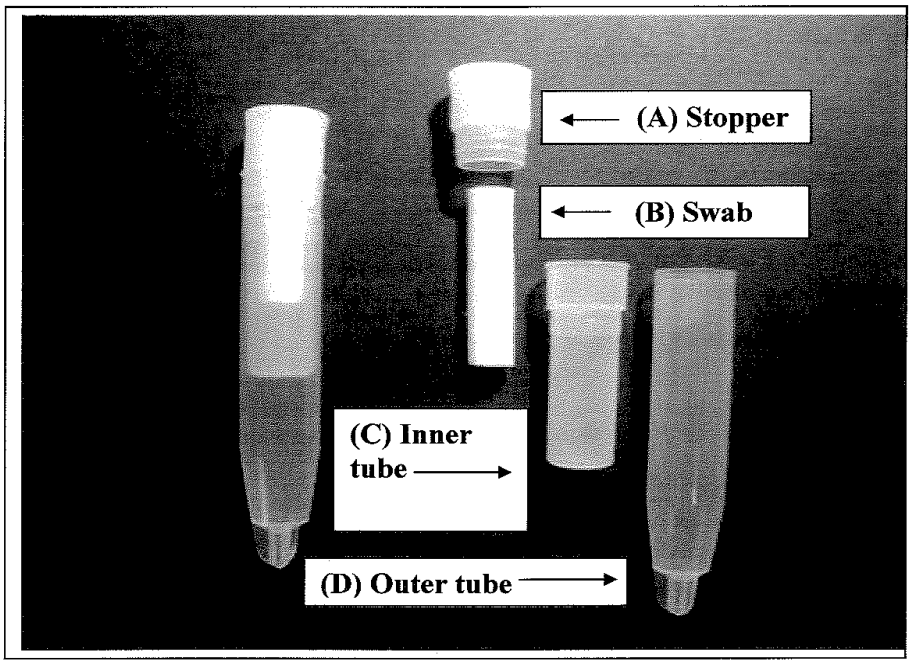
Instruction for collecting saliva with the Salivette

Collect saliva **three times a day**, twice in the **MORNING** and once in the **EVENING**

a) Morning Collection 1 – as soon as you wake up
b) Morning Collection 2 - 30 minutes after your first collection before you have breakfast or clean your teeth
c) Evening Collection before you go to bed, at least 30 minutes after you last ate or drank.

All salivettes are labelled with the day of collection.

The salivette is made up of four components as shown in the picture below



1) Hold the salivette at the rim of the Inner tube (c) and take out the stopper (a).
2) Take out the swab (b) from the salivette
3) Gently chew the swab for one minute. In any case, keep the swab in your mouth until you feel that you can no longer prevent yourself from swallowing the saliva produced.
4) Now return the saturated swab back into the inner tube (c), place the inner tube back into the outer tube and close the salivette firmly with the stopper (a).
5) Now please tick the allocated box in the attached checklist and repeat the above instruction at your next collection time.

Instruction for collecting saliva with the Salivette

Checklist for saliva collection

	Morning Collection	Morning collection 2	Evening Collection	Comments
Day 1 Date: _____	☼	☼	☆	
Day 2 Date: _____	☼	☼	☆	
Day 3 Date: _____	☼	☼	☆	

Your name: _____

Please place the 9 tubes of saliva back into the white padded envelope along with this checklist and seal the envelope once you have finished the 3-day collection. Please return the swabs and the checklist in the big FREEPOST envelope provided.

If you encounter any problems or have any queries please do not hesitate to contact me on ---------- and I will do my best to help.

Thank you very much for taking part in the saliva samples,

With best wishes,
Jo.

Appendix 5. 7: Cortisol protocol

Salivary cortisol radioimmunoassay protocol

DAY 1

- Label LP3 tubes:
    - 4 x Non-Specific Binding (NSB)
    - 4 x Total
    - 1 - 10 in triplicate for calibration curve
- Add 100ul buffer to NSB and tubes 2 - 10 of the calibration curve.
- Add 200ul buffer to NSB tubes.
- Add 200ul of cortisol standard (20ul stock in 10ml buffer, top tube 5ng/ml) and serially dilute.
    - Samples: 0.2ml saliva + 0.2ml buffer; 0.1ml/tube in duplicate.
- Add 100ul tracer (stock + Buffer to give c5000 cpm) to all tubes and vortex.
- Add 100ul of antibody (rabbit polyclonal, final titre 1:132 000) to all tubes except NSB and tracer.
- Vortex, cover in cling film and leave in cold room until next day.

DAY 2

- Make up dextran-coated charcoal solution and add 0.5ml to each tube except tracer and vortex.
- Spin for 15 minutes at 4ºC speed 4 (except tracer).
- Aspirate and count using crystal gamma counter.

Analytes:

Tracer: cortisol-3CMO-[125-I]histamine, Institute of Isotopes, Budapest, Hungary

Buffer: sodium citrate/sodium dehydrate orthophosphate dehydrate with 0.1% bovine serum albumin, pH3

Appendix 5. 8: Cytokine protocol

Blood collection protocol

- Take 5mls of blood with 150µl monoparin and keep on crushed ice.
- Centrifuged at 1500 rpm or 3000 rcf for 10 minutes at 4°C.
- Aliquot plasma into 5 x 200 µl aliquots. The remaining plasma should be aliquoted in 1ml volumes into appropriately labelled vials. Dispose of blood pellet.
- Snap freeze plasma placing the tubes into liquid nitrogen.
- Store samples at -80 until analysed.

Assay protocol:

1. **Defrost samples and aliquot into eppendorfs**. Spin for 3 minutes at 2.5rpm and keep on ice until required for assay.

2. **Addition of human serum cytokine assay diluent:** Dispense 25µL of human serum cytokine assay diluent into each well. Pipette to the bottom of the plate so as to allow the fluid to cover the entire bottom of the well. A slight tap may be necessary to allow the fluid to settle to the bottom. Seal the plate with an adhesive plate seal and incubate for 30 minutes with vigorous shaking (300-1000 rpm) at room temperature.

3. **Addition of sample or calibrator:** Dispense 25 µL of each calibrator or sample solution into a separate well of the MSD plate. Seal the plate with an adhesive plate seal and incubate for 2 hours with vigorous shaking (300-1000 rpm) at room temperature.

4. **Wash and addition of detection antibody solution:** Wash the plate 3X with PBS + 0.05% Tween-20. Dispense 25µL of the 1X detection antibody solution into each well of the MSD plate. Seal the plate and incubate for 2 hours with vigorous shaking (300-1000 rpm) at room temperature.

5. **Wash and Read:** Wash the plate 3X with PBS + 0.05% Tween-20. Add 150 µL of 2X read buffer T to each well of the MSD plate. Analyze the plate on the MSD SECTOR® Imager. Plates may be read immediately after addition of Read Buffer. Note: Bubbles in the fluid will interfere with reliable reading of the MULTI-SPOT plate. Use reverse pipetting techniques to insure bubbles are not created when dispensing the read buffer.

Data analysis

Assay results were saved into excel files. In total 9 plates were carried out. Plates 1-4 were carried out over two years and kit analytes were from different batches. Plates 5-9 were carried out in quick succession and were all from the same batch. Due to the different batch analytes the inter assay CV for plates 1-4 reached >100% with an average of 56%. This was deemed too high to give meaningful results in a clinical population.

Samples with an intra assay coefficient of variation (CV) from plates 1-4 were repeated in later plates as were a random selection of 3 samples from each plate with CV's of less than 10%. The repeated samples with CV's of less than 10% in plates 1-4 and 5-9 were used to calculate the ratio between the results from the first plates and plate 5 (assay result from plate 1-4 divided by assay result from plate 5) which was used to assign a fiddle factor for each cytokine from each plate (one for IL6, IL1ß, TNFα and IFNγ for each plate). The fiddle factors for plate 5 were comparable to the fiddle factors for plates 6-9 and the ratios were comparable across different samples, indicating that the results from assays 1-4 are consistent, thus it would be appropriate to use a fiddle factor. Therefore the following fiddle factors were applied to plates 1-4:

Assay number	IL6	IL1ß	IFNγ	TNFα
1	1.07	3.27	3.89	1.42
2	1.60	3.06	4.04	1.57
3	0.32	0.76	0.34	0.47
4	4.67	4.39	10.97	5.66

Fiddle factors for each cytokine

For the majority of samples (151) results from assays 5-9 could be used (where the inter assay CV was <11%). Fifty-eight samples (38%) were from assays 1-4 using the fiddle factor.

In the case of IL1ß many samples were below the lower limit of detection, in which case the level of the lowest limit of detection was entered. This was also the case in a few results for IFNγ where the same rule was applied.

Appendix 6. 1: Representativeness of recruited sample

		Not recruited, N(%)	Recruited, N(%)	OR (95% CI)
Diagnosis				
	HN	45 (73.77)	62 (60.78)	
	CR	16 (26.23)	40 (39.22)	0.55 (0.27-1.11)
Sex				
	M	36 (59.02)	56 (54.90)	
	F	25 (40.98)	46 (45.10)	1.18 (0.62-2.25)
Age	N	61	102	
	Mean (sd)	68.50 (11.75)	64.94 (13.74)	0.98 (0.95-1.00)
Marital status				
	Married (reference)	27 (64.29)	56 (58.33)	
	Cohabiting	0	9 (9.38)	
	Widowed	2 (4.76)	10 (10.42)	
	Divorced	4 (9.52)	120 (10.42)	
	Single	9 (21.43)	11 (11.46)	
	Missing	19	6	$\chi^2(4)=7.21$, $p=0.13$ ∓
Married				
	Yes	27 (64.29)	65 (67.71)	
	No	15 (35.71)	31 (32.29)	0.86 (0.40 to 1.85)
Ethnicity				
	White (reference)	45 (77.59)	87 (85.29)	
	Other	13 (22.41)	15 (14.71)	
	Missing	3	0	0.60 (0.26-1.37)

Not recruited includes patients who were uncontactable before their treatment and patients who declined participation. N=number; OR=Odds Ratio, CI= confidence interval. ∓ Chi^2 reported due to empty cells.

Appendix 6. 2: Alphas for all questionnaires in prospective study

Scale	Alpha	Scale	Alpha
CTQ – EA	0.79	CTQ – EN	0.86
CTQ – PA	0.86	CTQ – PN	0.57
CTQ – SA	0.92	CTQ-L	0.76
CTQ total	0.90		
EPQ – N	0.86	EPQ-Ex	0.87
EPQ-P	0.51	EPQ-L	0.82
Cope – self destruction	0.67	Venting	0.63
Active	0.87	Positive reframing	0.77
Denial	0.76	Planning	0.96
Substance use	0.79	Humour	0.91
Emotional support	0.87	Acceptance	0.59
Instrumental support	0.83	Religion	0.85
Behavioural disengagement	0.62	Self-blame	0.45

Scale	Alpha			
	T1	T3	T4	T5
HADS-A	0.84	0.88	0.89	0.85
HADS-D	0.82	0.81	0.87	0.87
HADS-T	0.87	0.90	0.91	0.87
Global QoL	0.89	0.88	0.90	0.91
Physical	0.86	0.83	0.83	0.85
Role	0.91	0.87	0.94	0.85
Emotional	0.80	0.89	0.92	0.81
Cognitive	0.72	0.63	0.56	0.51
Social	0.90	0.84	0.84	0.82
Fatigue	0.87	0.81	0.86	0.77
Nausea/vomiting	0.57	0.61	0.34	0.22
Pain	0.85	0.85	0.84	0.84
HN pain	0.70	0.68	0.84	0.66
HN swallowing	0.82	0.73	0.88	0.78
HN senses problems	0.76	0.72	0.55	0.72
HN speech problems	0.74	0.75	0.57	0.65
HN social eating	0.81	0.89	0.94	0.91
HN social contact	0.86	0.83	0.88	0.85
HN less sexuality	0.93	0.91	0.98	0.98
CR anxiety	0.75	0.64	0.61	0.11
CR body image	0.37	0.73	0.89	0.86
CR micturition problems	0.88	0.75	0.64	0.14
CR abdominal/pelvic pain	0.54	0.36	Too little variation for one answer	0.87
CR defaecation problems	1.00	0.37	0.64	0.37
CR faecal incontinence	0.74	Too few completions	0.12	0.47

Appendix 6. 3: Representativeness of T2 sample

Baseline characteristic		T2 data N (%)	No T2 data N (%)	OR (95% CI)
Age	N	20	70	
	Mean (sd)	70.86 (12.47)	63.96 (12.15)	0.95 (0.90-1.00)
IL6 T1	N	67	8	
	Mean (sd)	3.45 (3.86)	1.59 (0.62)	
	Median	2.11	1.59	1.45 (1.10-1.90)

OR=Odds ratio. CI= confidence interval

Appendix 6. 4: Representativeness of T3 sample

Baseline characteristic		T3 data N (%)	No T3 data N (%)	OR (95% CI)
Age	N	16	74	
Mean (sd)		72.38 (8.59)	64.01 (12.74)	0.94 (0.90-0.98)
Comorbidity rating				
	0	2 (14.29)	39 (56.52)	
	1	7 (50.00)	15 (21.74)	
	2	5 (35.71)	15 (21.74)	
	Missing	2	5	0.44 (0.24-0.82)
IL6 T2	N	7	63	
	Mean (sd)	46.28 (55.66)	8.68 (7.70)	
	Median	11.35	6.80	0.94 (0.90-0.99)
TNFα T2	N	64	7	
	Mean (sd)	4.22 (2.17)	8.33 (3.85)	
	Median	3.79	6.08	0.63 (0.51-0.79)
IFNγ T2	N	64	7	
	Mean (sd)	2.94 (7.04)	21.06 (50.61)	
	Median	1.26	1.89	0.97 (0.95-0.99)
CRP T2	N	64	7	
	Mean (sd)	54.73 (56.60)	132.86 (110.59)	
	Median	36.39	97.95	0.99 (0.98-1.00)

Appendix 6. 5: Representativeness of T4 sample

Baseline characteristic		T4 data N (%)	No T4 data N (%)	OR (95% CI)
Comorbidity rating				
	0	5 (26.32)	36 (56.25)	
	1	7 (36.84)	15 (23.44)	
	2	7 (36.84)	13 (20.31)	(As trend)
	Missing	4	3	0.51 (0.28-0.93)
IL6 T2	N	12	58	
	Mean (sd)	34.64 (44.38)	7.85 (6.45)	
	Median	11.15	5.93	0.72 (0.87-0.97)
TNFα T2	N	59	12	
	Mean (sd)	4.10 (2.01)	7.22 (3.83)	
	Median	3.78	5.93	0.67 (0.54-0.83)
IFNγ T2	N	59	12	
	Mean (sd)	3.08 (7.31)	12.84 (38.74)	
	Median	1.28	1.40	0.98 (0.96-1.00)
CRP T2	N	59	12	
	Mean (sd)	47.78 (46.31)	134.43 (100.40)	
	Median	31.76	106.83	0.98 (0.97-0.99)
IL6 T3	N	54	3	
	Mean (sd)	2.17 (1.64)	10.11 (12.42)	
	Median	1.67	3.43	0.73 (0.64-0.83)
IFNγ T3	N	55	3	
	Mean (sd)	2.88 (4.60)	1.40 (0.16)	
	Median	1.26	1.40	1.32 (1.11-1.58)
CRP T3	N	54	4	
	Mean (sd)	8.05 (16.88)	61.09 (115.50)	
	Median	3.39	4.2	0.98 (0.97-0.99)

Appendix 6. 6: Representativeness of T5 sample

Baseline characteristic		No T5 data N (%)	T5 data N (%)	OR (95% CI)
Comorbidity rating				
	0	6 (26.09)	35 (58.33)	
	1	8 (24.78)	14 (23.33)	
	2	9 (39.13)	11 (18.33)	
	Missing	4	3	0.46 (0.25-0.82)
TNFα T1	N	55	21	
	Mean (sd)	3.65 (1.57)	4.41(1.98)	
	Median	3.26	3.87	0.78 (0.61-1.00)
IL6 T2	N	16	54	
	Mean (sd)	28.68 (39.56)	7.62 (6.48)	
	Median	11.27	5.56	0.92 (0.87-0.92)
TNFα T2	N	55	16	
	Mean (sd)	3.98 (1.85)	6.85 (3.70)	
	Median	3.78	5.54	0.66 (0.54-0.82)
IFNγ T2	N	55	16	
	Mean (sd)	2.17 (2.63)	13.50 (35.21)	
	Median	1.19	1.66	0.94 (0.90-0.99)
CRP T2	N	55	16	
	Mean (sd)	47.47 (47.40)	133.87 (94.58)	
	Median	31.61	88.66	0.99 (0.98-0.99)
IL6 T3	N	52	5	
	Mean (sd)	2.21 (1.67)	6.54 (10.04)	
	Median	1.72	1.98	0.73 (0.64-0.83)
IFNγ T3	N	53	5	
	Mean (sd)	2.96 (4.67)	1.19 (0.35)	
	Median	1.31	1.24	1.65 (1.06-2.58)
CRP T3	N	52	6	
	Mean (sd)	8.20 (17.18)	42.14 (94.18)	
	Median	3.39	3.50	0.98 (0.97-1.00)

Appendix 6. 7: All variables tested – results for T5 only

Baseline characteristic	OR (95% CI)
Gender	2.06 (0.81-5.29)
Diagnosis	0.67 (0.27-1.68)
Age	0.98 (0.94-1.02)
BMI	0.92 (0.79-1.06)
Ethnicity	0.55 (0.16-1.92)
Marital status	$\chi^2(4)=8.06$, p=0.09
T stage	0.73 (0.78-1.11)
N stage	0.78 (0.45-1.36)
Presence of metastases	0.54 (0.11-2.61)
Surgery	1.17 (0.10-13.51)
Chemotherapy	1.1 (0.36-3.34)
Radiotherapy	1.24 (0.39-3.95)
Comorbidity rating	**0.46 (0.25-0.83)***
Smoking	$\chi^2(4)=0.92$, p=0.92
Alcohol	$\chi^2(4)=1.16$, p=0.56
Alcohol abuse	$\chi^2(4)=0.21$, p=0.64
HADS-D baseline∓	0.96 (0.85-1.08)
HADS-A baseline∓	0.99 (0.89-1.11)
Global Qol baseline	1.01 (1.00-1.04)
HADS-D T3∓	0.90 (0.77-1.06)
HADS-A T3∓	0.91 (0.80-1.05)
Global Qol T3	1.02 (0.99-1.05)
HADS-D T4∓	0.91 (0.75-1.10)
HADS-A T4∓	0.93 (0.76-1.14)
Global Qol T4	1.03 (0.99-1.08)
Life events T3	0.96 (0.66-1.40)
IL6 T1	0.90 (0.77-1.02)
IL6 T2	**0.92 (0.86-0.99)***
IL6 T3	0.82 (0.64-1.04)
Neuroticism	1.05 (0.89-1.25)
Emotional abuse	1.17 (0.75-1.82)
Physical abuse	1.52 (0.52-4.46)
Sexual abuse	1.20 (0.92-2.34)
Physical neglect	1.00 (0.72-1.42)
Emotional neglect	0.89 (0.86-1.05)

* P<0.05 ∓ Test for trend – no significant effect when treated as categorical variable.

Appendix 6. 8: Cases for possible and probable depression as indicated by HADS-D thresholds

	Score	CR N (%)	HN N (%)	Significance
HADS-D T1	0-7	29 (87.88)	46 (86.79)	
	8-10	2 (6.06)	5 (9.43)	
	≥ 11	2 (6.06)	2 (3.77)	$\chi^2(2)=0.77$, p=0.52
HADS-D T3	0-7	19 (76.00)	34 (73.91)	
	8-10	4 (16.00)	4 (8.70)	
	≥ 11	2 (8.00)	8 (17.39)	$\chi^2(2)=1.79$, p=0.41
HADS-D T4	0-7	16 (66.67)	31 (73.81)	
	8-10	4 (16.67)	3 (7.14)	
	≥ 11	4 (16.67)	8 (19.05)	$\chi^2(2)=1.46$, p=0.48
HADS-D T5	0-7	18 (81.82)	33 (80.49)	
	8-10	3 (13.64)	4 (9.76)	
	≥ 11	1 (4.55)	4 (9.76)	$\chi^2(2)=0.69$, p=0.71
HADS-A T1	0-7	20 (58.82)	31 (58.49)	
	8-10	9 (26.47)	13 (24.53)	
	≥ 11	5 (14.71)	9 (16.98)	$\chi^2(2)=0.10$, p=0.95
HADS-A T3	0-7	17 (68.00)	31 (67.39)	
	8-10	5 (20.00)	8 (17.39)	
	≥ 11	3 (12.00)	7 (15.22)	$\chi^2(2)=0.18$, p=0.91
HADS-A T4	0-7	15 (62.50)	28 (66.67)	
	8-10	3 (12.50)	7 (16.67)	
	≥ 11	6 (25.00)	7 (16.67)	$\chi^2(2)=0.75$, p=0.69
HADS-A T5	0-7	14 (63.64)	32 (78.05)	
	8-10	6 (27.27)	6 (14.63)	
	≥ 11	2 (9.09)	3 (7.32)	$\chi^2(2)=1.66$, p=0.44

Appendix 6. 9: Differences in HADS-D scores compared to baseline after adjusting for global QoL

Cancer group N*		ß(CI)	P value
CR	(ref) T1		
102 (34)	T3	1.20 (-0.15 to 2.54)	0.081
	T4	1.23 (-0.57 to 3.02)	0.181
	T5	0.60 (-0.65 to 1.86)	0.347
	Global QoL	-0.09 (-0.12 to -0.05)	<0.0005
HN	(ref) T1		
178 (56)	T3	1.25 (0.18 to 2.32)	0.022
	T4	1.09 (0.04 to 2.13)	0.041
	T5	0.45 (-0.51 to 1.42)	0.357
	Global QoL	-0.09 (-0.11 to -0.07)	<0.0005
All	(ref) T1		
280 (90)	T3	1.24 (0.433 to 2.06)	0.003
	T4	1.14 (0.23 to 2.06)	0.014
	T5	0.51 (-0.24 to 1.26)	0.183
	Global QoL	-0.09 (-0.011 to -0.07)	<0.0005

*N=total data, number in parentheses is number of patients.

Appendix 6. 10: HADS-D scores at each data wave

	CR		HN		Significance
	N	Mean (sd) Median	N	Mean (sd) Median	
HADS-D T1	34	3.32 (4.03) 1.5	53	3.49 (3.45) 3	z=0.31, p=0.76
HADS-D T3	25	4.89 (3.72) 5	45	5.24 (4.19) 4	z=0.25, p=0.81
HADS-D T4	25	5.17 (4.61) 3	42	4.83 (4.19) 3	z=-0.12, p=0.90
HADS-D T5	22	4.14 (3.81) 2	41	3.95 (3.98) 3	z=-0.07, p=0.95
HADS-A T1	34	6.00 (4.19) 6	53	6.52 (4.01) 6	z=0.50, p=0.62
HADS-A T3	25	5.98 (4.51) 6	45	6.09 (4.48) 5	z=0.02, p=0.99
HADS-A T4	25	6.61 (5.26) 6	42	6.05 (3.93) 6	z=-0.17, p=0.87
HADS-A T5	22	5.55 (4.23) 5	41	5.17 (3.15) 4	z=-0.25, p=0.81

Appendix 6. 11: Global QoL scores at each data wave

	CR		HN		Significance
	N	Mean (sd) Median	N	Mean (sd) Median	
Global QoL T1	32	63.54 (25.82) 66.67	52	68.11 (23.67) 75	z=0.97, p=0.33
Global QoL T3	25	62.67 (25.47) 66.67	45	60.74 (22.86) 66.67	z=-0.45, p=0.66
Global QoL T4	24	60.76 (24.63) 58.33	41	65.85 (20.31) 66.67	z=0.87, p=0.39
Global QoL T5	21	65.87 (27.63) 58.33	40	68.75 (19.41) 75.00	z=0.39, p=0.70

Appendix 6. 12: Differences in HADS-D scores compared to baseline

Cancer group N*		Standardised ß (CI)	P value
CR	(ref) T1		
105 (34)	T3	1.44 (-0.06 to 2.95)	0.060
	T4	1.46 (-0.32 to 3.24)	0.107
	T5	0.46 (-1.20 to 2.12)	0.587
HN	(ref) T1		
181 (56)	T3	1.97 (0.84 to 3.09)	0.001
	T4	1.75 (0.73 to 2.77)	0.001
	T5	0.97 (-0.05 to 1.98)	0.061
Total	(ref) T1		
286 (90)	T3	1.78 (0.88 to 2.67)	<0.0005
	T4	1.64 (0.73 to 2.55)	<0.0005
	T5	0.78 (-0.09 to 1.66)	0.080

*N=total data, number in parentheses is number of patients.

Appendix 6. 13: Differences in global QoL scores compared to baseline

Cancer group N*		ß (CI)	P value
CR	(ref)	T1	
102 (34)		T3 -2.96 (-13.99 to 8.07)	0.599
		T4 -4.45 (-15.37 to 6.48)	0.425
		T5 0.52 (-10.88 to 11.93)	0.928
HN	(ref)	T1	
178 (56)		T3 -7.35 (-12.96 to -1.73)	0.010
		T4 -5.48 (-11.67 to 0.71)	0.083
		T5 -2.82 (-8.49 to 2.85)	0.330
Total	(ref)	T1	
280 (90)		T3 -5.84 (-11.16 to -0.53)	0.031
		T4 -5.05 (-10.62 to 0.52)	0.076
		T5 -1.56 (-6.96 to 3.84)	0.571

*N=total data, number in parentheses is number of patients.

Appendix 6. 14: Differences in global QoL scores compared to baseline after adjusting for HADS-D

Cancer group N*		ß(CI)	P value
CR	(ref)	T1	
		T3 3.52 (-5.61 to 12.65)	0.450
		T4 2.50 (-9.03 to 14.02)	0.671
		T5 3.90 (-4.56 to 12.37)	0.366
	HADS-D	-3.82 (-5.04 to -2.61)	<0.0005
HN	(ref)	T1	
		T3 -1.37 (-6.68 to 3.94)	0.613
		T4 0.10 (-6.15 to 6.35)	0.976
		T5 0.06 (-5.67 to 5.79)	0.984
	HADS-D	-3.13 (-3.87 to -2.39)	<0.0005
All	(ref)	T1	
		T3 0.41 (-4.31 to 5.13)	0.864
		T4 1.05 (-4.69 to 6.78)	0.721
		T5 1.38 (-3.40 to 6.15)	0.572
	HADS-D	-3.46 (-4.09 to -2.82)	<0.0005

*N=total data, number in parentheses is number of patients.

Appendix 8. 1: Cortisol descriptives

Cortisol variable	CR		HN		Mann Whitney sign test significance
	N	Mean (sd) Median₮	N	Mean (sd) Median₮	
Morning cortisol	28	2.10 (1.45) 1.70	30	2.04 (1.17) 1.96	z=0.34, p=0.74
Morning cortisol +30mins	28	2.63 (1.02) 1.92	31	2.82 (1.79) 2.30	z=0.62, p=0.53
Morning rise	28	0.53 (1.33) 0.36	30	0.80 (1.25) 0.65	z=0.69, p=0.49
Evening cortisol	29	0.71 (0.73) 0.52	30	0.74 (0.64) 0.57	z=0.55, p=0.59
Overall cortisol level	29	2.01 (1.22) 1.68	31	2.13 (1.19) 2.04	z=0.64, p=0.52

₮ All values given in ng/ml.

Appendix 8. 2: Robust standard error parameters for cortisol and QoL regressions

Patient group	Cortisol measure	Time	N	ß(CI)	P value
CR	Morning rise cortisol	T1 QoL	27	5.80 (0.69 to 10.92)	0.028
CR	30 minute waking	T4 QoL	21	5.01 (0.49 to 9.53)	0.032
CR	Morning rise cortisol	T4 QoL	21	5.16 (0.28 to 10.03)	0.039
CR	Morning rise cortisol	T5 QoL	18	6.64 (1.49 to 11.78)	0.015
CR	Overall cortisol	QoL	87 (28)	4.93 (0.67 to 9.19)	0.023
HN	Evening cortisol	T3 QoL	23	-16.65 (-25.26 to -8.04)	0.0001
HN	Evening cortisol	T5 QoL	23	-15.83 (-21.41 to -10.24)	<0.0005

Appendix 8. 3: Inflammatory descriptives

Inflammatory marker	CR		HN		Mann Whitney sign test significance
	N	Mean (sd) Median[Ŧ]	N	Mean (sd) Median[Ŧ]	
IL-6 T1	27	4.08 (4.22) 2.45	48	2.78 (3.32) 1.71	z=-1.48, p=0.14
IL-6 T2	**30**	**19.78 (31.06) 10.84**	**41**	**7.25 (6.11) 5.33**	**z=-2.03, p=0.04**
IL-6 T3	21	2.16 (1.85) 1.55	36	2.84 (3.99) 1.87	z=0.83, p=0.41
TNF-α T1	**28**	**4.73 (1.98) 4.64**	**48**	**3.35 (1.31) 3.00**	**z=-3.49, p<0.001**
TNF-α T2	**30**	**6.12 (3.04) 5.40**	**41**	**3.53 (1.66) 3.22**	**z=-4.06, p<0.0005**
TNF-α T3	22	4.23 (1.49) 4.11	36	4.34 (2.20) 3.68	z=-0.39, p=0.70
IFN-γ T1	28	1.35 (1.11) 0.93	48	1.35 (1.11) 0.93	z=-1.22, p=0.22
IFN-γ T2	30	8.11 (26.06) 1.32	41	2.25 (2.62) 1.30	z=-0.36, p=0.77
IFN-γ T3	**22**	**1.56 (2.12) 1.02**	**36**	**3.57 (5.34) 1.58**	**z=2.77, p=0.01**
CRP T1	28	16.25 (26.74) 4.02	47	9.60 (17.99) 2.50	z=-1.91, p=0.06
CRP T2	**30**	**86.28 (80.10) 66.18**	**41**	**44.97 (48.61) 31.61**	**z=-2.28, p=0.02**
CRP T3	22	9.54 (24.29) 2.03	36	13.04 (38.93) 3.85	z=1.83, p=0.07

Ŧ All values are in pg/ml

Appendix 8. 4: Significant changes in levels of inflammation over time

		CR		HN	
		N	ß (CI)	N	ß (CI)
IL6	T1	27		48	
	T2	29	16.00 (5.27 to 26.73)*	41	4.35 (2.63 to 6.08)*
	T3	21	1.03 (-1.32 to 3.39)	36	-0.08 (-1.49 to 1.34)
TNFα	T1	28		48	
	T2	30	1.43 (0.46 to 2.40)*	41	0.24 (-0.17 to 0.64)
	T3	22	0.10 (-0.48 to 0.69)	36	0.96 (0.40 to 1.51)*
IFNγ	T1	28		48	
	T2	30	5.13 (-3.75 to 14.01)	41	0.90 (0.17 to 1.62)*
	T3	22	0.66 (-1.94 to 3.26)	36	2.21 (0.48 to 3.95)*
CRP	T1	28		47	
	T2	30	71.00 (44.96 to 97.04)*	41	35.08 (21.89 to 48.26)*
	T3	22	1.13 (-11.69 to 13.95)	36	3.21 (-8.12 to 14.54)

*indicates significantly different (p<0.05) compared to T1

Appendix 8. 5: Robust standard error parameters for inflammatory markers and HADS-D at T3 in CR cancer patients

N	Marker	ß (CI)	P value
20	T1 IL6	0.50 (0.21 to 0.80)	0.004
21	T1 TNFα	0.95 (0.40 to 1.50)	0.002
21	T1 IFNγ	0.28 (0.19 to 0.38)	<0.0005
21	T1 CRP	0.12 (0.05 to 0.18)	0.002
23	T2 IFNγ	0.16 (0.11 to 0.21)	<0.0005
21	T3 IFNγ	0.50 (0.22 to 0.77)	0.001
21	Peri* IFNγ	0.34 (0.23 to 0.44)	P<0.0005

*Peri=perioperative rise (T2 – T1)

Appendix 8. 6: Robust standard error parameters for inflammatory markers and HADS-D at T3 in HN cancer patients

N	Marker	ß (CI)	P value
33	T3 IL6	0.38 (0.27 to 0.48)	<0.0005
33	T3 TNFα	0.78 (0.06 to 1.49)	0.034
33	T3 CRP	0.04 (0.03 to 0.05)	<0.0005

Appendix 8. 7: Robust standard error parameters for inflammatory markers and HADS-D at T4 in CR cancer patients

N	Marker	ß (CI)	P value
20	T1 IL6	0.63 (0.23 to 1.02)	0.004
21	T1 TNFα	1.04 (0.20 to 1.89)	0.018
21	T1 IFNγ	0.35 (0.24 to 0.45)	<0.0005
21	T1 CRP	0.12 (0.05 to 0.18)	0.002
23	T2 IFNγ	0.18 (0.12 to 0.24)	p<0.0005
23	T2 TNFα	1.02 (0.16 to 1.89)	0.022
22	T3 TNFα	1.09 (-0.08 to 2.26)	0.066
21	Peri* IFNγ	0.34 (0.05 to 0.66	0.025

*Peri=perioperative rise (T2 – T1)

Appendix 8. 8: Robust standard error parameters for inflammatory markers and HADS-D at T5 in CR cancer patients

N	Marker	ß (CI)	P value
20	T2 IFNγ	-0.52 (-1.04 to 0.00)	0.048
18	Peri* CRP	0.03 (0.00 to 0.05)	0.039
18	Peri* IFNγ	0.52 (-0.87 to -0.18)	0.006

*Peri=perioperative rise (T2 – T1)

Appendix 8. 9: Robust standard error parameters for inflammatory markers and HADS-D overall in CR cancer patients

N	Marker	ß(CI)	P value
88 (28)	T1 TNFα	0.80 (0.43 to 1.18)	<0.0005
88(28)	T1 IFNγ	0.19 (0.11 to 0.27)	<0.0005

Appendix 8. 10: Robust standard error parameters for inflammatory markers risk of DE6 in HN cancer patients

N	Marker	OR(CI)	P value
34	T3 IFNγ	0.61 (0.38-0.98)	0.040

Appendix 8. 11: Robust standard error parameters for inflammatory markers and T1 QoL in CR cancer patients

N	Marker	ß(CI)	P value
27	T1 TNFα	-5.66 (-10.62 to -0.70)	0.027
27	T1 CRP	-0.29 (-0.59 to 0.01)	0.057

Appendix 8. 12: Robust standard error parameters for inflammatory markers and T3 QoL in CR cancer patients

N	Marker	ß (CI)	P value
20	T3 IL6	-9.07 (-17.78 to -0.36)	0.042
21	T3 TNFα	-9.10 (-17.14 to -1.06)	0.029
21	T3 IFNγ	-4.13 (-5.92 to -2.33)	<0.0005

Appendix 8. 13: Robust standard error parameters for inflammatory markers and T3 QoL in HN cancer patients

N	Marker	ß (CI)	P value
37	T2 IL6	-1.47 (-2.68 to -0.27)	0.018
37	T2 CRP	-0.19 (-0.33 to -0.05)	0.009
33	T3 IL6	-2.78 (-3.34 to -2.23)	<0.0005
33	T3 TNFα	-5.37 (-9.95 to -0.78)	0.023
33	T3 CRP	-0.29 (-0.33 to -0.24)	<0.0005
36	Peri IL6	-1.72 (-2.98 to -0.45)	0.0009
35	Peri CRP	-0.22 (-0.35 to -0.08)	0.002

Appendix 8. 14: Robust standard error parameters for inflammatory markers and T4 QoL in CR cancer patients

N	Marker	ß (CI)	P value
23	T2 IFNγ	-0.50 (-0.79 to -0.22)	0.002
21	Peri* IFNγ	-1.44 (-2.33 to -0.54)	0.003

*Peri=perioperative rise (T2 – T1)

Appendix 8. 15: Robust standard error parameters for inflammatory markers and T5 QoL in CR and HN cancer patients

Cancer group	N	Marker	ß (CI)	P value
CR	19	T3 IFNγ	-3.41 (-6.92 to 0.11)	0.057
HN	36	T1 IFNγ	-4.04 (-7.03 to -1.04)	0.010
HN	36	T1 IL6	-1.13 (-2.40 to 0.13	0.077
HN	34	T2 IL6	-1.21 (-2.35 to -0.06)	0.040
HN	32	T3 IL6	-3.73 (-6.91 to -0.56)	0.023

Appendix 8. 16: Robust standard error parameters for inflammatory markers and overall QoL in CR cancer patients

N	Marker	ß (CI)	P value
86 (28)	T1 IFNγ	-0.78 (-1.33 to -0.23)	0.005
86 (28)	T1 CRP	-0.22 (-0.41 to -0.03)	0.027

Appendix 9. 1: Robust standard error parameters for associations between cortisol and inflammation

Group	N	Cytokine	Cortisol measure	ß (CI)	P value
CR	24	IL6	Waking +30 mins	0.62 (-0.04 to 1.29)	0.065
	25	IL6	PM	2.31 (0.40 to 4.22)	0.020
	25	IL6	Overall mean	0.96 (0.12 to 1.81)	0.027
	26	IFNγ	PM	0.73 (0.24 to 1.22)	0.005
HN	26	IFNγ	Waking	-0.33 (-0.65 to -0.02)	0.040
	26	IFNγ	Waking +30 mins	-0.18 (-0.37 to -0.01)	0.056
	27	IFNγ	Overall mean	-0.30 (-0.58 to -0.03)	0.032

Appendix 9. 2: Robust standard error parameters for associations between psychological and physiological markers in CR cancer patients

Psychological	Physiological	N	ß(CI)	P value
NE	Cortisol morning rise	19	-0.11 (-0.18 to -0.04)	0.005
CT	CRP T1	16	2.25 (0.17 to 4.33)	0.036
CT	TNFα T2	18	0.19 (0.08 to 0.30)	0.002
LE	TNFα T1	23	-0.28 (-0.53 tp -0.02)	0.003
LE	IL6 T1	22	-0.36 (-0.72 to 0.00)	0.052

Appendix 9. 3: Robust standard error parameters for associations between inflammation and fatigue and pain

Group	Marker	Symptom	N	ß (CI)	P value
CR	IFNγ T1	Fatigue T1	27	2.36 (1.65 to 3.08)	<0.0005
	CRP T1	Fatigue T1	27	0.57 (1.00 to 0.94)	0.004
	IFNγ T1	Fatigue T3	21	1.33 (0.74 to 2.58)	0.001
	CRP T1	Fatigue T3	21	0.66 (0.28 to 1.04	0.002
	IL6 T1	Pain T4	20	-2.27 (-3.96 to -0.57)	0.012
	TNFα T1	Pain T4	21	-4.67 (-8.21 to -1.13)	0.012
	IFNγ	Pain T4	21	-0.93 (-1.65 to -0.21)	0.014
	TNFα T2	Pain T5	20	6.66 (1.53 to 11.79)	0.014
HN	IFNγ T1	Pain T5	36	6.30 (0.13 to 12.46)	0.046
	IL6 T1	Pain T5	36	1.89 (0.00 to 3.79)	0.050
	CRP T2	Pain T3	37	0.22 (0.04 to 0.40)	0.017
	CRP T2	Pain T5	34	0.42 (0.15 to 0.68)	0.003
	IL6 T3	Pain T3	33	2.99 (1.98 to 4.00)	<0.0005
All	IL6 T2	Fatigue T3	59	1.25 (-0.03 to 2.54)	0.056
	IL6 T2	Fatigue T4	57	1.55 (0.53 to 2.57)	0.003
	IL6 T2	Fatigue T5	53	1.18 (0.23 to 2.13)	0.016
	CRP T2	Fatigue T3	60	0.19 (0.04 to 0.33)	0.011
	CRP T2	Fatigue T4	58	0.18 (0.05 to 0.31)	0.006
	CRP T2	Fatigue T5	54	0.17 (0.04 to 0.31)	0.014